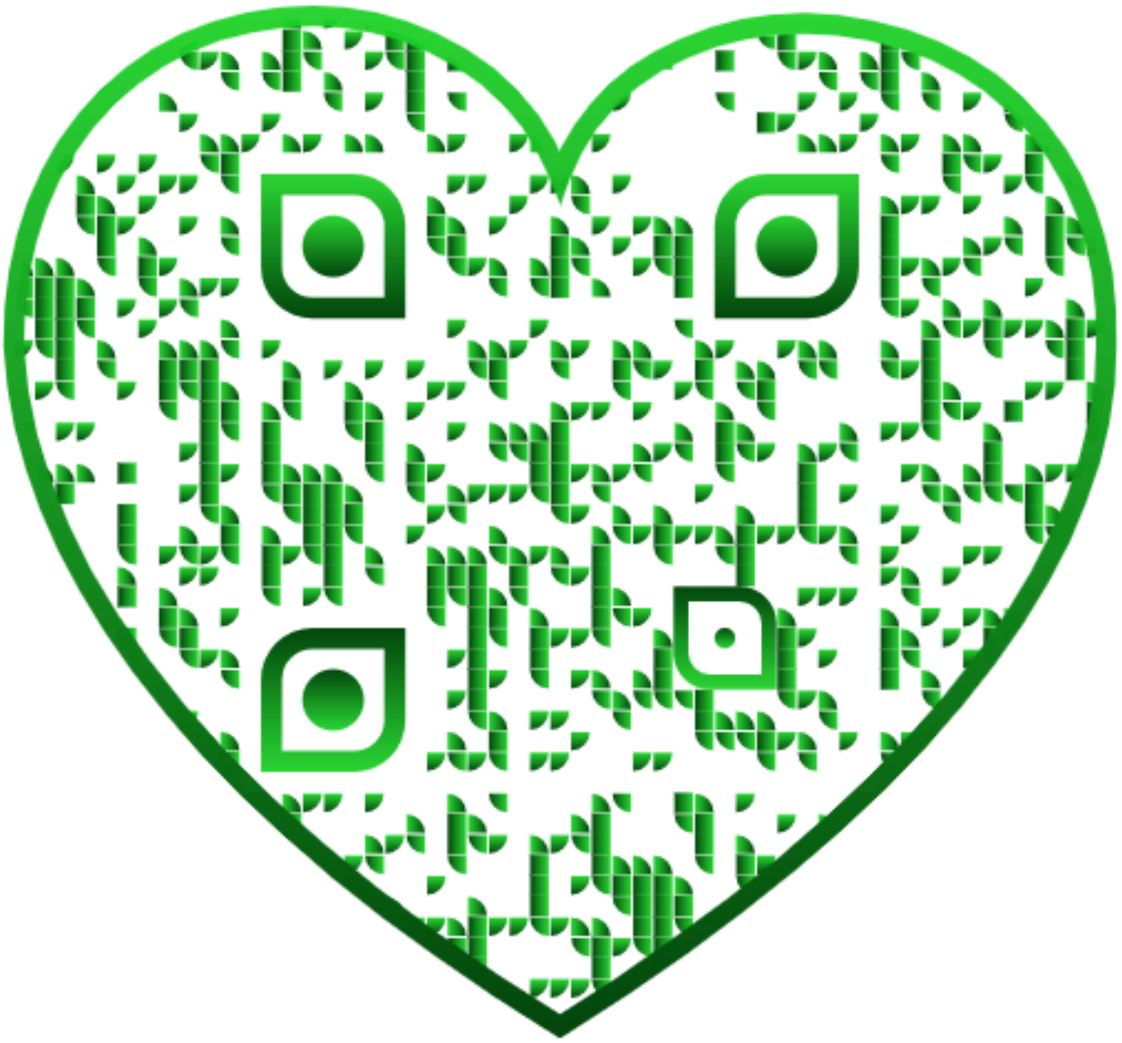
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الفهرس ومحتويات الملف بالترتيب

General pharmacology

ANS

CVS+Diuretic

GIT

CNS

Endocrine system

Chemotherapy

Respiratory system

Autacoids

Drug used in gloucoma

General pharmacology

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Assist. Professor of pharmacology and Toxicology

General pharmacology

- **Pharmacology:** It is the science that study the effects of drugs on living system.
- **Drug:** Substance used for diagnosis, prophylaxis or treatment of disease.
- **Pharmacokinetics:** This science study the movement of the drug within the body; it includes (absorption, distribution, metabolism and excretion). It means ‘what the body does to the drug’.
- **Pharmacodynamics:** This science deals with Mechanism & pharmacological Actions of drugs. It means ‘what the drug does to the body’.
- **Pharmacotherapeutics:** This science deals study of therapeutic uses and doses of drugs.
- **Toxicology:** is a branch of pharmacology which deals with the undesirable effect of chemical and drugs on living system.
- **Pharmacopoeia:** It is a book that contains a list of established and officially approved drugs having description of their physical and chemical characteristics with tests for their identification, purity, methods of storage**.**

General pharmacology

- **Adverse effects:** This term describes the unwanted drug effects and is sometimes referred to as "side effects" or "toxic effects".

- **Contraindications:** The diseases in which the drug should be avoided, e.g. Aspirin is contraindicated in peptic ulcer.

- **Drug Interactions:**

a) Drug-Drug interactions: when 2 or more drugs are prescribed to the patient, these interactions may be beneficial (favorable) or harmful (unfavorable).

b) Drug-Food interactions, e.g. MAO inhibitors (used in treatment of depression) interact with food containing tyramine as cheese and yoghurt and lead to serious and may be fatal elevation of arterial blood pressure.

General pharmacology

❖ Sources of Drug

❑ Natural source

- Plant e.g. Atropine is obtained from Atropa belladonna.
- Animals e.g. Heparin.
- Minerals e.g. ferrous sulfate, Iron.
- Microorganism e.g. Penicillin.

❑ **Semisynthetic drugs** e.g. Hydromorphone, hydrocodone

❑ **Synthetics sources** e.g. Sulfonamides. aspirin, paracetamol.

❑ **Biotechnology (genetic engineering):** Drugs are also produced by genetic engineering (DNA recombinant technology), e.g. human insulin, human growth hormone, hepatitis B vaccine.

❖ Names of drugs:

1. **Chemical name:** It describes the chemical structure of the drug. e.g. acetylsalicylic acid is the chemical name of aspirin.

2. **Generic name:** given by the official sources e.g. aspirin

3. **Trade name**: It is given by drug manufacturer, e.g. (Ecoprine)® is a brand name of aspirin

General pharmacology

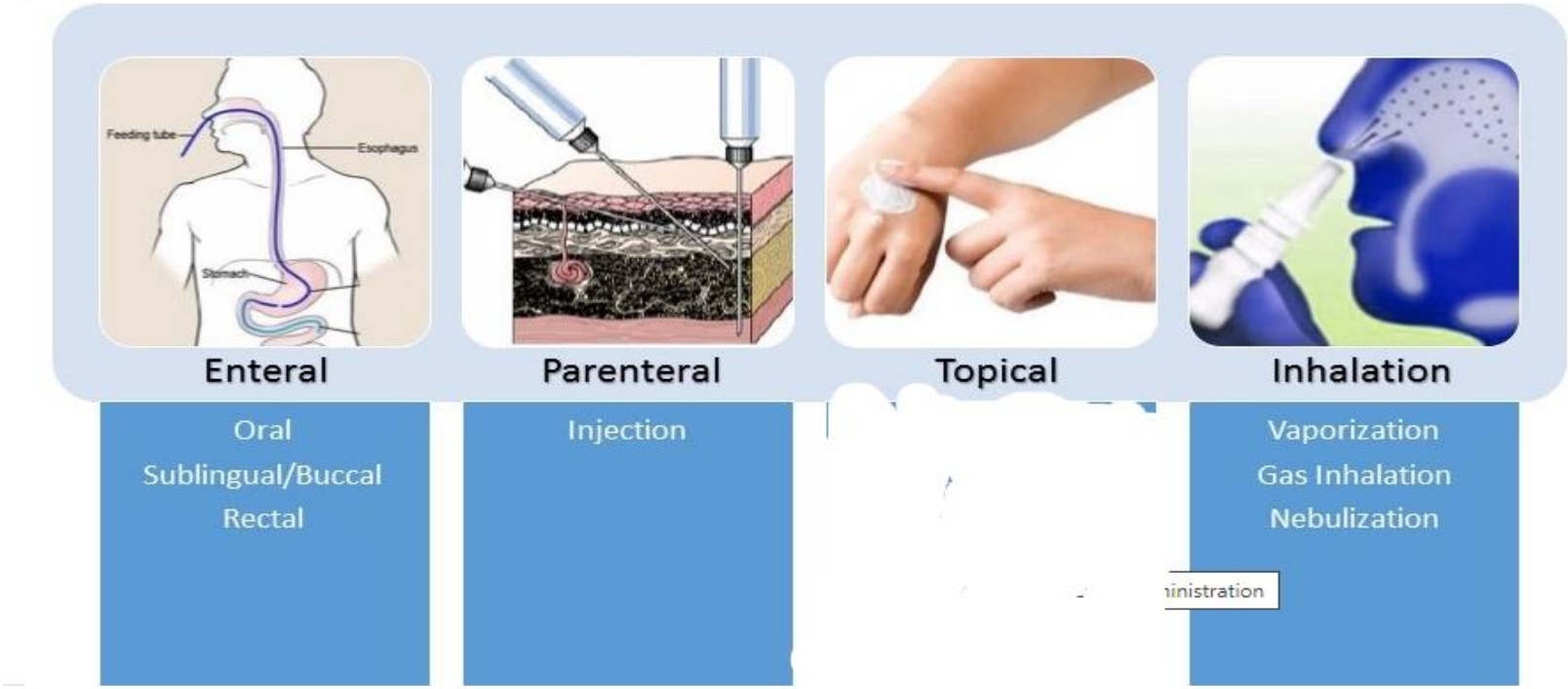
❖ Classes of drugs:

1) **Prescription only Medication**: Drugs that require a medical prescription to be dispensed.

2) **Over The Counter (OTC)** drugs: Used by the public without a prescription e.g. analgesics, laxatives, antitussive and antacids.

❖ Routes of drug-administration

- There are 4 main routes of drug administration: Enteral, Parenteral, Inhalation and Topical route.



❖ Routes of drug administration

1. **Enteral route:** drugs are given through GIT. It is either: Oral, Sublingual, Rectal

a) **Oral route:** It is the most common and acceptable route for drug administration. Dosage forms are tablet, capsule, syrup, mixture, etc.

❑ **Advantages:** Safer, Cheaper, Convenient for repeated and prolonged use, self-administered.

❑ **Disadvantages:**

• Not suitable for:

- Emergencies (Delayed onset of action).
- Unabsorbable drugs (e.g. aminoglycosides).
- Drugs that are destroyed by digestive juices (e.g. insulin).
- Drugs with extensive first-pass metabolism (e.g. lignocaine).
- Unconscious patients.
- Drugs that are destroyed by gastric acidity (e.g. Benzyl penicillin).
- Patients with severe vomiting and diarrhoea.

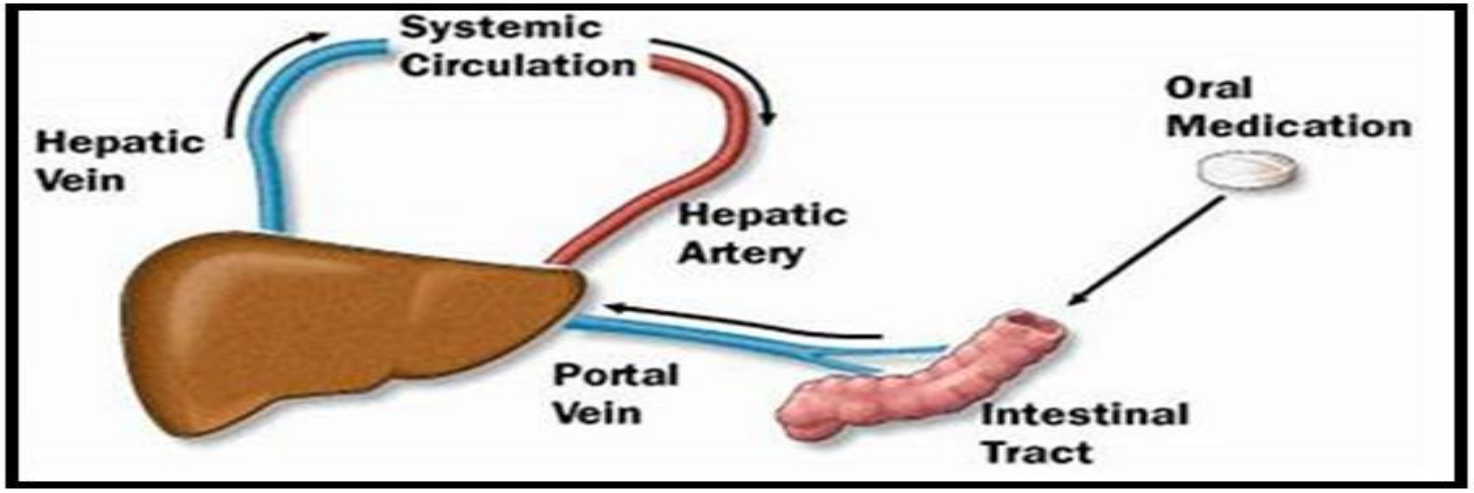
❖ **First pass effect:** Inactivation of part or whole of the drug before reaching the general circulation. (Gut or hepatic first pass effect)

a) **Gut first pass effect:** - Gastric acidity: e.g. Benzyl penicillin
- Digestive enzymes: e.g. insulin - Mucosal enzymes: Tyramine

a) **Hepatic first pass effect:** - Complete e.g. Nitroglycerine & lidocaine
- Partial: Propranolol & Morphine - Minimal: Atenolol

❖ **To overcome hepatic first pass effect:**

- If partial: increase the dose of the drug
- If complete: Use another route e.g. sublingual nitroglycerine & IV lidocaine.



b) Sublingual Route: The preparation is kept under the tongue. The drug is absorbed through the buccal mucous membrane and enters the systemic circulation directly, e.g. nitroglycerin for acute angina attack.

❖ **Advantages:**

- Rapid onset of action.
- Over dose effect can be avoided by spitting out the tablet.
- Avoids first-pass metabolism.
- Self-administration is possible.

c) Rectal Route: Drugs can be given in the form of solid (Suppository) or liquid (Enema).

❖ **Advantages**

- Useful in vomiting patients.
- Suitable for children and geriatrics
- Useful in irritant drugs on stomach and drugs that undergo first pass effect.

❖ **Disadvantages**

- Psychological many patient refuse this route
- Not suitable in diarrhea.

2. **Parenteral Routes:** All drugs must be sterile and pyrogen-free

A) Intravenous (IV) injection

- Most drugs should be slowly injected.
- Only aqueous solutions are allowed

❖ **Advantages**

- 100% bioavailability and Onset of action of drugs is faster; hence it is suitable for emergency.
- No first pass effect
- Useful for highly irritant drugs.
- Useful in unconscious patients.
- Useful for drugs not absorbed orally.
- Useful in vomiting..
- Large volumes can be given by I.V. infusion.

❖ **Disadvantages**

- Low safety (Allergic reaction as anaphylactic shock).
- Must be sterile.
- Transmission of diseases e.g. viral hepatitis C & AIDS.
- Required professional person.
- Not suitable for oily and suspended drugs to avoid embolism.

B) Subcutaneous (S.C.) route:

- The drug is injected into the subcutaneous tissues of the thigh, abdomen and arm, e.g. adrenaline, insulin, etc.
- More rapid and complete than oral and is suitable for non-irritant drugs

C) Intramuscular (IM) route:

- **Advantages**
- Absorption is more rapid as compared to oral route and S.C. but less than IV.
- Solutions, Suspensions, oily preparations, moderately irritant can be given by this route.

- **Disadvantages**
- Aseptic conditions are needed.
- Intramuscular injections are painful and may cause abscess.
- Self-administration is not possible.
- There may be injury to the nerves.

D) Intradermal (ID):

- The drug is injected into the layers of the skin, e.g. vaccination and drug sensitivity tests.

E) Other injection:

- **Intrathecal injection**: Drug is injected into the subarachnoid space (spinal anesthetics), e.g lignocaine.

- **Intracardiac injection** e.g. Adrenalin in cardiac arrest.

3. Inhalation: Volatile liquids and gases are given by inhalation for systemic effects, e.g. general anesthetics

❖ **Advantages:**
- Quick onset of action.
- Dose required is very less, so systemic toxicity is minimized.
- Amount of drug administered can be regulated.

❖ **Disadvantages:** Irritation of bronchi by some drugs-irregular dosage.

4. Topical route:

a) Skin:
- Ointments, creams, and powders are applied for local actions.
- Transdermal delivery system (TDS) as transdermal patches which are applied for systemic actions as nitroglycerin. It avoids 1st pass and has long duration

b) Mucous membranes (Nose, Ear, Eye, Mouth).
- Used for local actions, e.g. eye drops in glaucoma.
- May be used for systemic actions as nasal vasopressin (ADH) in treatment of diabetes insipidus.

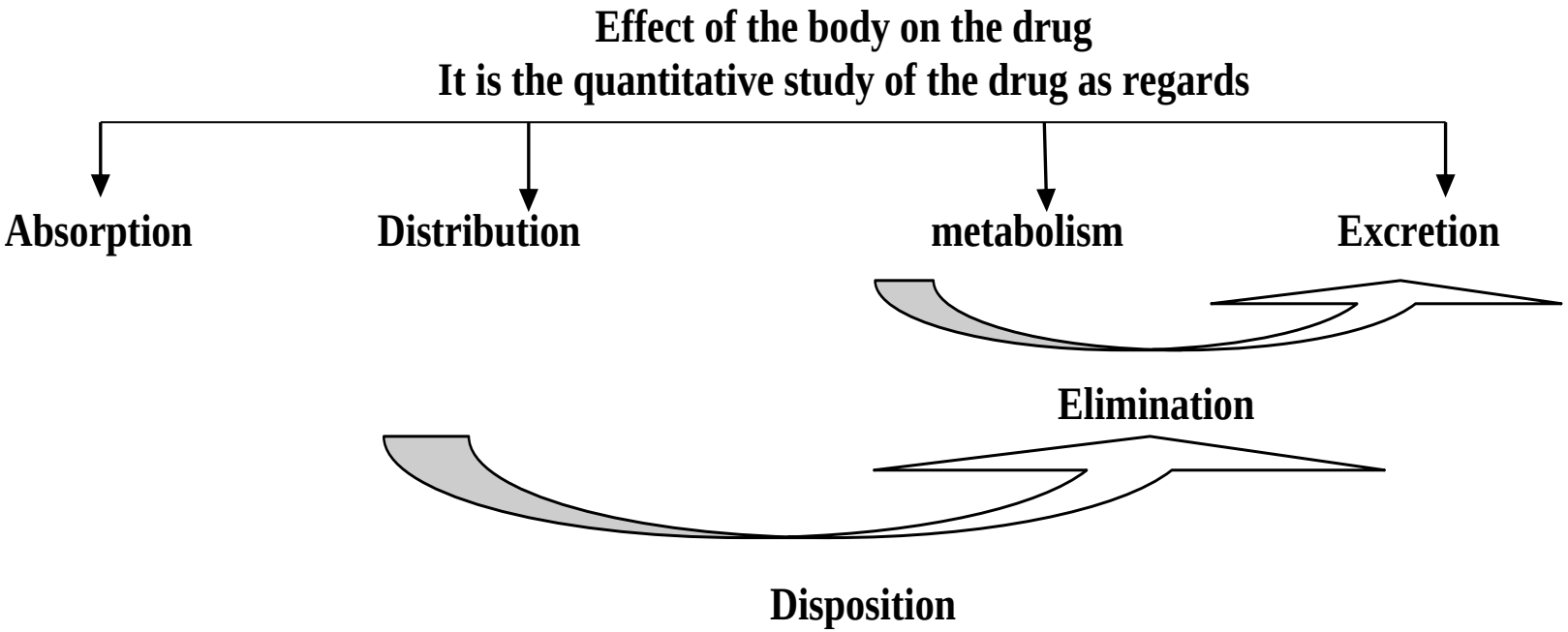
General pharmacology

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Pharmacokinetics

Pharmacokinetics



1. Absorption:

- It is the passage (transfer) of the drug from the site of administration to the systemic circulation.

Pharmacokinetics

- All biological membranes are made up of lipid bilayer. Drugs cross various biological membranes by the following mechanisms:

1. **Passive diffusion**:

a) **Simple diffusion**

- The drug passes through bilayer lipid of cell membrane.
- low molecular weight (LMW) lipophilic (most drugs)
- The drug moves along the concentration gradient from high to low concentration.
- No need for energy or carrier.
- The absorption depends on lipid solubility, ionization and molecular weight of drugs

b) Filtration

- Through pores depends on water solubility & osmotic pressure.
- No need for energy or carrier.

2. Specialized transport

a) Facilitated diffusion

- High molecular weight (HMW) hydrophilic.
- From high concentration to low concentration.
- Needs carrier but doesn`t need energy.
- e.g. transport of glucose across muscle cell membrane by a transporter GLUT4.

b) Active transport

- From low concentration to high concentration against the concentration gradient.
- Needs carrier and energy.
- e.g. transport of sympathomimetic amines into neural tissue, and absorption of levodopa from the intestine.

c) Endocytosis: Pinocytosis and phagocytosis:

- Transport drugs of exceptionally large size.
- Engulfment of a drug molecule by the cell membrane.
- As absorption of (vitamin B12+intrinsic factor) complex.

Pharmacokinetics

❖ Factors affecting absorption of drugs:

A - Factors related to drugs:

1- **Degree of ionization**:
- Highly ionized drugs (polar) are poorly absorbed. (As gentamicin)
- Non-ionized drugs (non-polar) are highly absorbed. (As thiopental)

2- **Degree of lipid solubility**: Higher lipid solubility → increase absorption.

3- **Effect of pH:**

- Acidic or basic drugs are less ionized and more absorbable in media with the same pH rang
- Weak acidic drugs are highly unionized (HA) in acidic media (as stomach) → ↑ absorption. (as aspirin and barbiturates)
- Weak basic drugs are highly unionized (B) in basic media (as intestine) → ↑ absorption. (as amphetamine and ephedrine)

Pharmacokinetics

4- **Valence:** Less valence more absorption, Ferrous iron (Fe2+) > Ferric Iron (Fe3+).

6- **Pharmaceutical preparation**:

- Solution > suspension > tablet.
- ↑ Rate of dissolution and disintegration → ↑ absorption.

B- Factors related to patient:

1- **Route of administration**: IV> Inhalation>sublingual > rectal> IM > SC > oral > skin.

2- **Available surface area**: ↑ Surface area → ↑ absorption.
Absorption from intestine is better than stomach.

3- **Blood flow to the absorption site**: ↑ Blood flow → ↑ absorption.

- Shock and heart failure → ↓ absorption.
- Adrenaline SC → vasoconstriction → ↓ absorption of other drug.

4- **Specific factors**: Intrinsic factor for Vit. B12 absorption.

C-Factors specific for absorption from gastrointestinal tract

1) **Gastric emptying**: May be increase or decrease absorption (depend on drugs)

- Metoclopramide → ↑ emptying → ↑ absorption of paracetamol (rapid rate of dissolution and disintegration) & ↓ absorption of digoxin (slow rate of dissolution and disintegration).
- Atropine → ↓ gastric emptying → the reverse effect.

2) **Motility of GIT.** ↑ Motility (diarrhea) → ↓ absorption.

3) **Presence of food and other drugs in GIT**:

- Food → ↓ absorption of most drugs (ampicillin, cephalosporins , rifampicin , tetracycline, levodopa).
- Milk (Ca+2) → ↓ absorption of tetracycline.
- Tannic acid from tea → ↓ absorption of iron.
- Food is useful in irritant drugs as aspirin to decrease irritation.
- Fatty meal increases the absorption of griseofulvin
- Drug-drug interactions.

4) **First pass effect**: (decrease bioavailability)

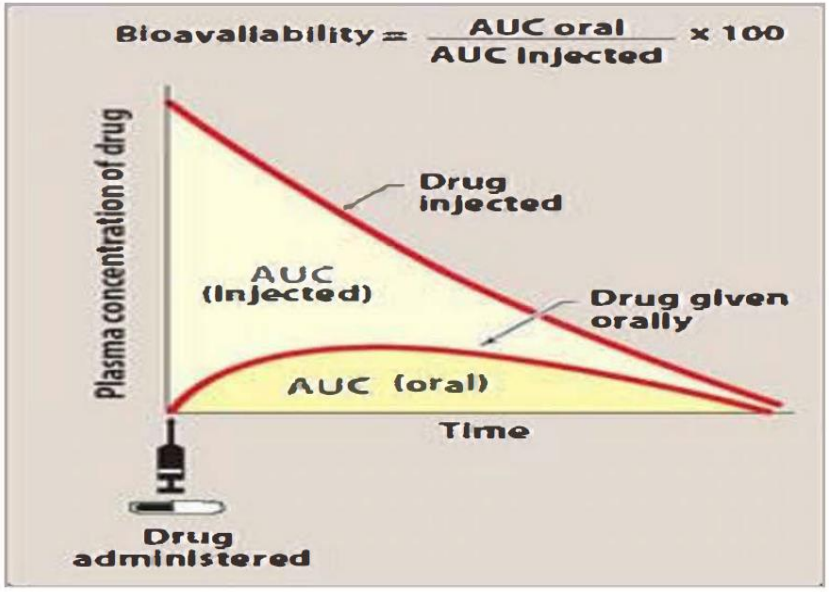
❖ Estimation of drug absorption

❖ **Bioavailability:** The rate of administrated drug that reaches the systemic circulation in a chemically unchanged form.

❖ Determining bioavailability is important for calculating drug dosages for no intravenous routes of administration.

- IV root is associated with availability 100% because the drug reaches the central compartment with no change.
- If two formulations of the same drug produce equal bioavailability, they are said to be **bioequivalent.**.

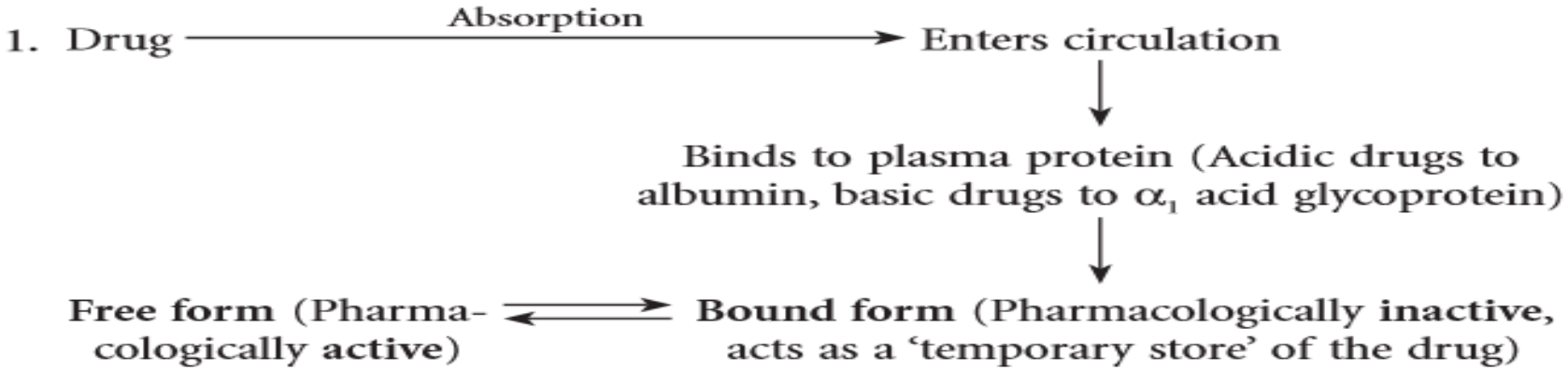
Oral bioavailability = AUC oral / AUC IV X 100



Pharmacokinetics

2. Distribution

- The transfer of drugs from the blood stream to the interstitium and/or the tissues


1. Drug
Absorption
Enters circulation
Binds to plasma protein (Acidic drugs to albumin, basic drugs to α_1 acid glycoprotein)
Free form (Pharmacologically active)
Bound form (Pharmacologically inactive, acts as a 'temporary store' of the drug)

❖ The distribution of drug depends on

- **Lipid solubility**: Unionized with small molecular weight are widely distributed.
- **Blood flow:** Drugs are distributed in organs with high blood flow e.g. general anesthetics are concentrated in nervous system (lung > liver > brain).
- **General health of patient:** Plasma proteins are decreased in liver and kidney diseases leading to increase drug distribution and decrease storage.
- **Degree of binding to plasma proteins**. (↑ Protein binding → ↓ distribution)

Pharmacokinetics

❖ Binding of drugs to plasma proteins (PP):

1. They include:

   - **Very highly bound**: sulfonamides, non-steroidal anti-inflammatory drugs
   - **Highly bound**: Oral anticoagulants, oral hypoglycemic (antidiabetic), furosemide(diuretic),

2. A fraction of most drugs binds reversibly to plasma proteins.
3. Albumin is the major binding plasma protein.
4. The bound fraction of the drug NOT Active, NOT Filtered, NOT Metabolized & NOT Excreted.
5. The more binding → the longer duration.
6. Hypoalbuminemia → ↓ PP binding. As in liver diseases.
7. Drugs with high affinity for plasma proteins as sulfonamides,

- Aspirin and sulfonamides displace digoxin → ↑ digitalis toxicity.
- Aspirin and sulfonamides displace sulphonylureas (as Tolbutamide) → ↑ hypoglycemia.
- Aspirin and sulfonamides displace warfarin → ↑ bleeding.

Pharmacokinetics

❖ Blood brain barrier (BBB):

- Lipid cellular barrier.
- Only the lipid-soluble and unionized form of drugs can pass through BBB and reach the brain, e.g. (tetracycline, quinolones, refampicin, clindamycin, sulfonamides) pass and used in prophylactic & treatment of brain infection.
- Meningitis (inflammation of meninges) → ↑ permeability of some drugs through BBB as penicillin (used only in treatment of brain infections and not used in prophylaxis (intact BBB).

❖ Placental barrier to fetus:

- The lipid membrane between mother and fetus is called placental barrier.
- Lipid soluble non-ionized drugs can pass easily and affect the fetus/newborn, e.g. anaesthetics, morphine, corticosteroids, etc.
- Some drugs that pass placental barrier can cause teratogenicity or malformations especially in the first trimester (Organogenesis period) as phenytoin and tetracyclines
- substances with high molecular weight like insulin cannot cross the placental barrier.

❖ **Selective distribution**: Some drugs have special affinity for specific tissue as:

- Calcium in bones.
- Iodide in thyroid gland.
- Digitalis in heart.
- Arsenic in hair

Pharmacokinetics

❖ Apparent volume of distribution: (Vd)

$$Vd = \frac{\text{Total amount of drug in the body (D)}}{\text{Concentration of drug in plasma (C)}}$$

- Vd is the apparent volume of fluid into which an administrated drug is distributed.
- Small Vd = drugs are highly bound to plasma proteins.
- High Vd = drugs are highly unbound to plasma proteins.

- Helps in estimating the total amount of drug in the body. (D = Vd x C)

- Vd is important to determine the loading dose or the additional dosage needed to achieve the desired concentration.

Loading dose = Vd x desired concentration
Additional dosage needed = Vd x (C2 - C1)

C1 = initial concentration.
C2 = higher desired concentration.

3. Metabolism ('Biotransformation)

- Chemical alteration of the drug AIMING to convert: Drugs (Active, Non-ionized & Lipid soluble) Metabolite → (Inactive, Ionized & water soluble) → Easily excreted in urine & bile.
- The metabolism occurs mainly in liver and also present in other organs as lung, GIT, kidney, skin and plasma

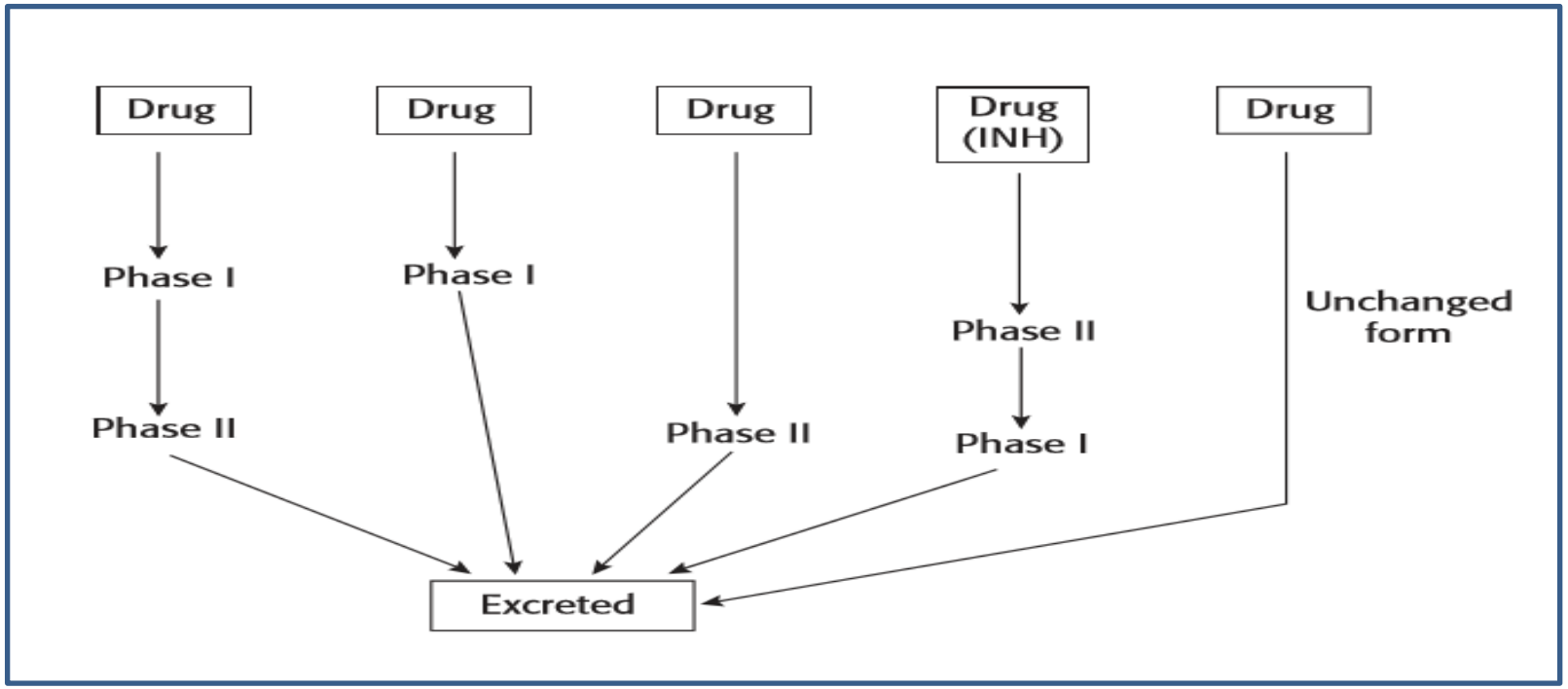
❖ Pathways of Drug Metabolism

- Drug metabolic reactions are grouped into two phases.
- They are phase I or no-synthetic reactions and phase II or synthetic reactions

1. **Phase I reactions:** (non-synthetic)
   - Oxidation: ethanol → acetaldehyde → acetic acid.
   - Reduction: chloral hydrate → trichloroethanol.
   - Hydrolysis: acetylcholine → acetic acid + choline.

2. Phase II reactions: (synthetic or conjugation)

- Glucuronic acid: as paracetamol & chloramphenicol.
- Acetic acid (acetylation): as isoniazid & sulfonamides.
- Methylation: as noradrenalin.
- Sulfates: as phenols.
- Glycine: as aspirin.



❖ Drug-Metabolizing Enzymes

1. Hepatic microsomal enzymes metabolism (HME):

- In hepatic smooth endoplasmic reticulum.
- The reactions (catalyzed by cytochrome P450) are oxidation, reduction, hydrolysis and conjugation with glucuronidation only.
- their activity is increased or decreased by drugs known as HME inducers and HME inhibitors; respectively.
- Activity is unstable.

2. Non-hepatic microsomal enzymes metabolism:

- In cytoplasm and mitochondria of liver cells, skin, GIT, lungs, and in plasma.
- All the reactions except glucuronidation.
- Can not induced or inhibited by drugs.
- Activity is stable.

❖ Factors Affecting Hepatic Microsomal Enzyme activity:

1. **Age:** The activity of HME is lower in extremities of age; i.e. neonates (especially if premature) and old age, so they should be treated with lower doses than adults.

2. **Genetic variations:** genetic abnormalities may result in defective or abnormal enzymes; e.g. genetic defect in pseudocholinesterase enzyme greatly reduces metabolism -and increases the action- of succinylcholine (skeletal muscle relaxant) and may lead to "apnea". This abnormal drug response due to genetic defect is known as "idiosyncrasy.

3. **Sex (Gender)**: Male sex hormones (androgens) act as HME inducers whereas female sex hormones (estrogen and progesterone) act as HME inhibitors. This is an important cause why females receive lower doses than males (of the same age and weight).

4. **Health status**: As liver diseases → ↓ enzyme activity

Pharmacokinetics

❖ **Hepatic microsomal enzyme (HME) inducers:** → ↑ metabolism rate → ↓ the action of other drug (Oral anti-coagulants, Oral hypoglycemic & Oral contraceptive drugs).

- Examples HME inducer: phenobarbitone, rifampicin, carbamazepine and phenytoin.

❖ **Hepatic microsomal enzyme (HME) inhibitors:** → ↓ metabolism rate → ↑ the action of other drugs (warfarin, digitalis, oral hypoglycemic and theophylline) and may leading to toxicity. That is why we should reduce the dose of warfarin, digitalis, oral hypoglycemics and theophylline if given with HME inhibitors.

- Examples HME inhibitor: chloramphenicol, cimetidine, omeprazole, ketoconazole and ciprofloxacin.

Pharmacokinetics

4. Excretion:

- Removal of the drug and its metabolite from the body is known as drug excretion.
- The main channel of excretion of drugs is the kidney; others include lungs, bile, faeces, sweat, saliva, tears, milk, etc.

❖ **Renal excretion: by**:

- Glomerular filtration: - For water soluble and non-bound drugs as mannitol.
- Active tubular secretion: - For many drugs as penicillin and furosemide.
- Passive tubular reabsorption: - For lipid soluble drugs as some hormones.

❖ The excretion of drugs affected by change in urinary pH:

- Alkalization of urine (by $NaHCO_3$ or Na citrate) → ↑ excretion of acidic drugs as aspirin or phenobarbitone.
- Acidification of urine (by NH_4Cl or Vit. C) → ↑ excretion of basic drugs as ephedrine or amphetamine.
- These facts are clinically useful in treatment of acute drug toxicity by increasing their excretion in urine through changing the pH of urine.

Pharmacokinetics

- Faeces: Drugs that are not completely absorbed from the GI tract are excreted in faeces, e.g. purgatives like senna, cascara, et

- Lung excretion:
- Alcohol and volatile general anaesthetics such as ether, halothane, enfl urane and isofl urane are excreted via lungs.

- Skin excretion:
- Through sweat gland:
- As rifampicin and vit. B1 → red discoloration.

- Breast milk: Drugs taken by lactating women may appear in the milk. It has acidic pH, hence basic drugs like tetracycline, chloramphenicol, morphine, diazepam, etc. remain in ionized form and are excreted through milk; hence they may affect the suckling infant.

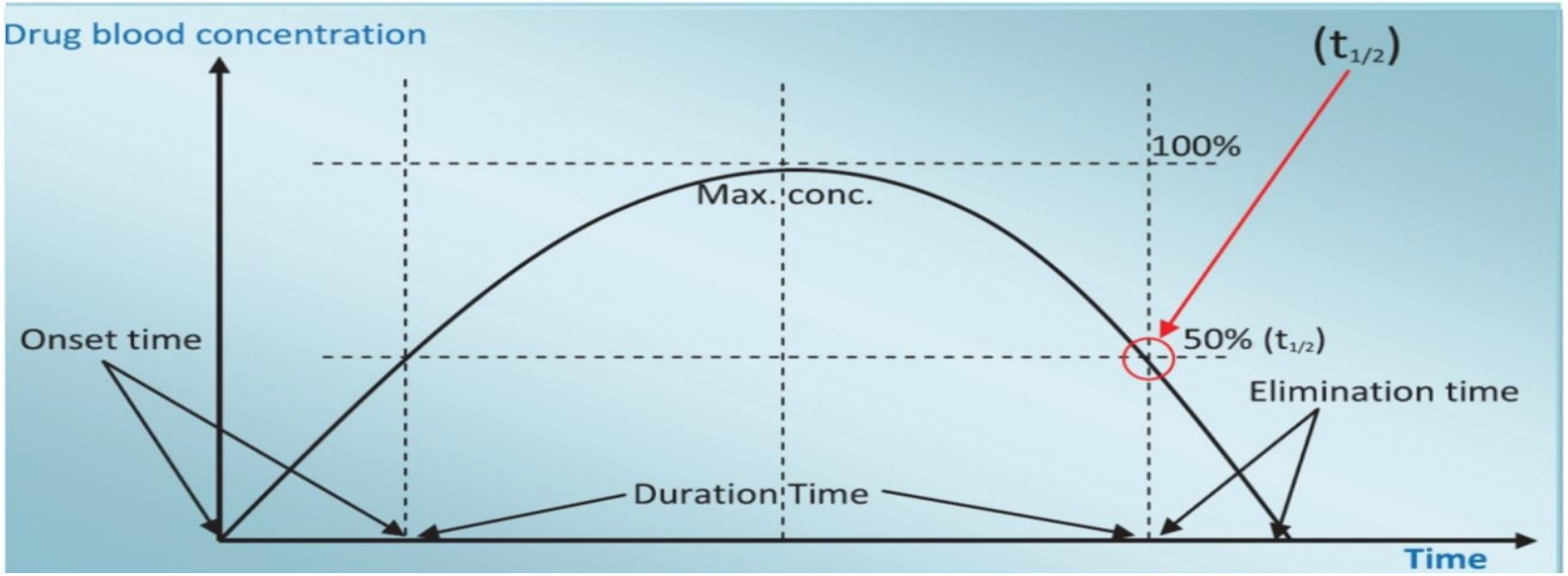
Pharmacokinetics

❖ **Plasma half-life =Elimination half-life ($t_{1/2}$):**

- It is the time needed by the body to reduce the plasma concentration of any drug by 50% (i.e. it is the time needed to eliminate 50% of the drug in plasma).
- Most drugs reach Css concentration after 4-S $t_{1/2}$.
- For most drugs almost the entire drug (> 95%) is eliminated within 4-S $t_{1/2}$.
- It is useful to determine the frequency of drug administration.

❖ **Onset of action:** Time from administration to blood level reaching minimal effective concentration (MEC).

❖ **Duration of action:** Time plasma concentration remains greater than MEC.



General pharmacology

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Pharmacodynamics

Pharmacodynamics

❖ **Pharmacodynamics:** It is usually referred to as "the effect of drug on the body

❖ **It includes:**

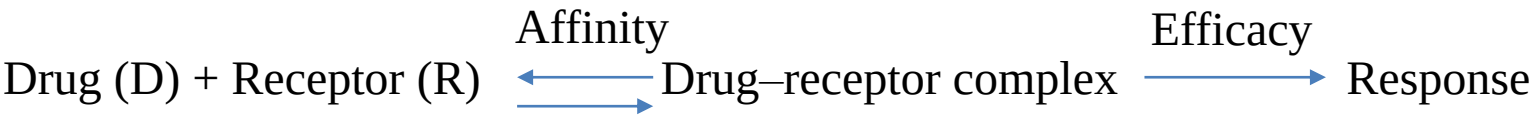
A) Mechanism of action.

B) Pharmacological actions.

A) Mechanism of drug action

1. **Physical action:** as Adsorption: (activated charcoal in gases and toxins).
2. **Chemical action:** as neutralization: (NaHCO3 in hyperacidity)
3. **Cytotoxic action:** (stop cell division): As anticancer drugs.
4. **Action on ion channel**: Local anesthetics (Na channel blockers)
5. **Action on enzymes**: as Captopril (ACE inhibitor)
6. **Action on receptors**: (most drugs)

- **Receptors:** protein macromolecules present on the surface or within the cell which the **Ligand** (drug or neurotransmitters) binds and interacts to produce cellular changes.



Pharmacodynamics

- **Affinity**: is the ability of the drugs to bind to the receptor to form Drug/Receptor complex.

- **Efficacy (intrinsic activity)** = Ability of D/R complex to produce pharmacological action.

- **Agonist:** A drug that is capable of producing pharmacological action after binding to the receptor.

  - Agonist has high affinity + high intrinsic activity (e.g. morphine and adrenaline).

  ❖ **Types of agonists:**

  - **Full agonist:** produces maximum effect. (as phenylepherine on α1 receptors).
  - **Partial agonist:** has affinity and lower efficacy than full agonist. (Can acts as agonist or antagonist). As acebutolol on β1 receptors.
  - **Inverse agonist:** has full affinity but produces inverse effect compared to agonist. As B- carboline on benzodiazepine receptors

- **Antagonist**: are drugs that block the receptors thus preventing the action of the agonist

  - Antagonist has high affinity but No efficacy (e.g. naloxone and atropine). It produces receptor blockade.

Pharmacodynamics

❖ Types of antagonists:

1) Competitive antagonist:

- The antagonist competes with the agonist on the same site of the receptor.
- Displaced by increase the dose of the agonist.
- Potency (agonist binding) is decreased with the same Emax.
- As atropine and acetylcholine on muscarinic receptors.

2) Non-competitive antagonist:

- The antagonist acts on different site of the receptors.
- Not displaced by increase the dose of the agonist.
- Same potency but decreased Emax.
    - **Reversible Antagonists**: binds reversibly and short acting. As succinylcholine.
    - **Irreversible Antagonists**: binds irreversibly and long acting. As phenoxybenzamine.

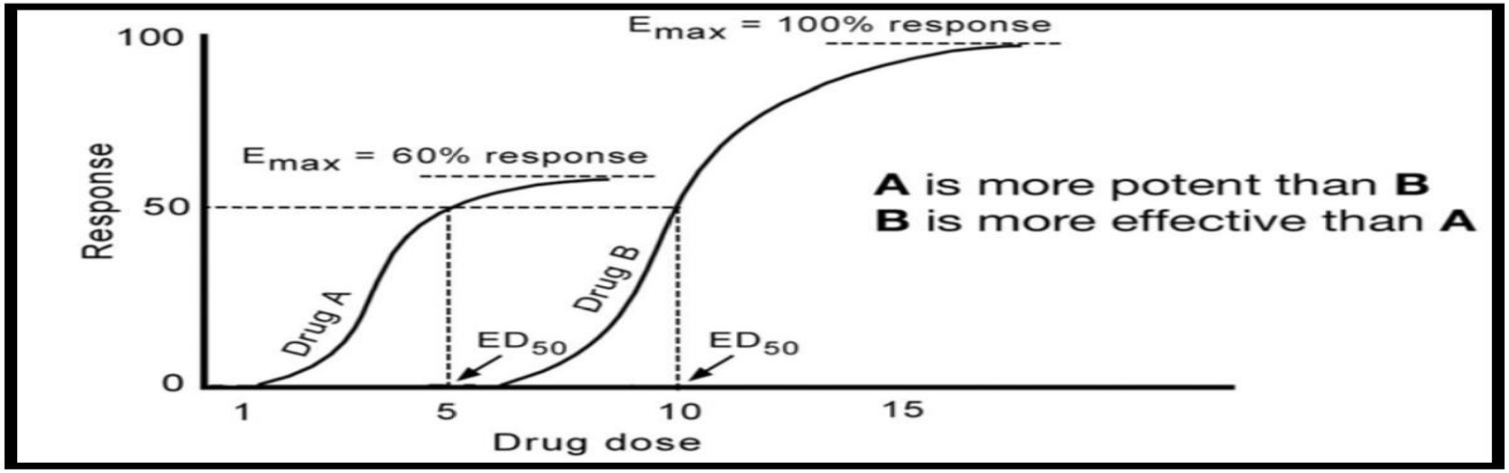
- **Emax:** (Maximal Efficacy) The maximum effect of the drug. For example, morphine is more efficacious than aspirin as an analgesic → Efficacy

- **Effective concentration50 (EC50)**: The concentration of the drug that produce 50% of Emax. → Potency

Pharmacodynamics

- **Potency:** It is a measure of the amount of drug required to produce an effect.
  - The lower the dose required for a given response, the more potent. e.g. the analgesic dose of morphine (10 mg) more potent than pethidine (100 mg).
  - The more potent the drug, the smaller the EC50.

❖ Dose- Response Curves:



❖ Classification of receptors:

1. Ligand-gated ion channel:

- Change in membrane potential or ionic concentration within the cell.
- Response is very rapid (about milliseconds).
- Acetylcholine + nicotinic receptors → open ↑ Na+ channel → depolarization.
- Benzodiazepines + GABAA receptors → ↑ Cl- influx → hyperpolarization.

Pharmacodynamics

2. G-protein-linked receptors: The response from seconds to minutes.

- **The common types of G-proteins:**

- Gs (stimulatory) → ↑ adenylate cyclase → ↑ cAMP (second messenger) → open Ca^{+2} channel → ↑ Ca^{+2} influx. (As β1-agonists)

- Gi (inhibitory) → ↓ adenylate cyclase → ↓ cAMP → close Ca^{+2} channel → ↓ Ca^{+2} influx. (As α2-agonists)

- Gq (stimulatory) → ↑ phospholipase C → ↑ inositol triphosphate and diacetyl glycerol (second messengers) → ↑ Ca^{+} influx. (As α1-agonists and M1,3-agonists)

3. Enzyme linked (tyrosine kinase-linked) receptors.

- The response from minutes to hours.
- As insulin receptors.

4. DNA-linked receptors (intracellular receptors)

- For lipid soluble drugs that can diffuse across the cell membrane, enter the nucleus and bind to intra-nuclear receptors.
- Slow onset response from hours to days.
- As corticosteroids and thyroxin.

Pharmacodynamics

❖ Receptors regulation:

- Receptors can be regulated by various mechanisms resulting in either their **up-regulation** or **downregulation**
- Under normal conditions; the number of receptors is fixed. This may vary in the following conditions:

1) **Down-regulation** → Long use of an agonist → ↓ the number (and sensitivity) of receptors, → Tolerance: Acquired drug Resistance. The drug produces its usual therapeutic effect in unexpected high dose

2) **Up-regulation** → Long use of an antagonist → ↑ the number (and sensitivity) of receptors → Intolerance(sensitivity): The drug produces its usual adverse effects in unexpected low dose.

Pharmacodynamics

Dosage of drugs (Posology):

- **Therapeutic dose:** It is the dose required to achieve therapeutic effect in an adult male of average weight (70 Kg.).
- **Loading dose:** the initial large dose that give rapid therapeutic plasma concentration.
- **Maintenance dose:** Small daily dose required to replace eliminated drug from the body to maintain the achieved therapeutic plasma concentration.
- **Minimal effective dose:** the lowest dose required to produce a therapeutic effect.
- **Maximal Tolerated dose:** It the maximum dose that can be safely administered without inducing toxic effects.
- **Effective Dose (ED50):** it is the dose that induces a specific therapeutic effect in 50% of experimental animals.

Pharmacodynamics

- **Toxic Dose (TD_{50}):** It is the dose that induces a particular toxic effect in 50% of experimental animals.

- **Lethal Dose (LD_{50}):** It is the dose that induces death in 50% of experimental animals.

- **Therapeutic Index (T.I):** It is a measure of drug safety; the higher the index the safer the drug.

$$TI = \frac{\text{Median lethal dose } (LD_{50}) \text{ of the drug}}{\text{Median effective dose } (ED_{50}) \text{ of the drug}}$$

Therapeutic Index (margin of safety) = ↑ T.I → ↑ safety margin for the drug.

  - A good guide to determine & compare **SAFETY** of drugs
  - Drugs with large therapeutic index (as penicillins) are safer than drugs with narrow therapeutic index (as digitalis, lithium, phenytoin, warfarin).

General pharmacology

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Dosage of drugs

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Dosage of drugs

❖ Factors affecting dosage and action of drugs:

1. Age, Body Weight & Surface area:

- **Adult dose**: for persons (18-60 years) and weight about 70 kg.

- **Infant dose** (< 1 year) $= \frac{\text{Adult dose X weight in Kg}}{70}$ (Clark's Formula)

- **Child dose** (1 -12 year) $= \frac{\text{Adult dose X Age in years}}{\text{Age in years + 12}}$ (Young' Formula)

  Or Child dose $= \frac{\text{Adult dose X Age in years}}{20}$ (Dilling's Formula)

- **Geriatrics (Elderly> 60 years):**
  - Use 3/4 of the adult dose (60-80 years)
  - 1/2 of the adult dose (over 80 years).

- Surface area is more accurate in calculating doses for children & infants.

Dosage of drugs

2. Sex (Gender):

- Females may need smaller dose than males due to high fat content and the inhibitory effect of estrogen on liver microsomal enzymes (HME Inhibitor)

- Some drugs avoided in pregnancy (teratogenic drugs), lactation (Purgatives, Tetracyclines & Chloramphenicol).and during menstruation (e.g. aspirin).

3. Route and Time of Administration:

- Oral dose > SC > IM > IV.
- If drug is irritant → Use after meals
- If drug is sedative → Use at bed time
- CNS stimulant drugs not be given at bed time → cause insomnia. As ephedrine

4. Tolerance:

- Failure of response to the usual dose of a drug.

- **Types of tolerance:**

  1. **Congenital tolerance**:
     - Racial: Ephedrine is not mydriatic in Negroes.
     - Species: Rabbits are resistant to atropine.

2. **Acquired tolerance:**

- ↓ Response of drugs after their long use (reversible). As morphine and nitrates.
- Cross tolerance: between similar drugs as ethanol and diethyl ether.
- Tachyphylaxis (acute): sudden decrease in response as ephedrine on blood pressure.
- Bacterial resistance to antibiotics.

❑ Mechanism of acquired tolerance:

a) **Pharmacokinetic causes**: →↓ concentration of the drug at the site of action may be due to decreased absorption, increased metabolism (HME inducers) and excretion, e.g. barbiturates, carbamazepine, nicotine increase their own metabolism.

b) **Pharmacodynamic causes**: long use of drugs leads to "down-regulation" of receptors or depletion of endogenous transmitters. e.g. Repeated use of opioids, barbiturates

5. Dependence:

It is either:

a) **Psychic dependence = Habituation:**

- Psychic dependence.
- Sudden stop of the drug→ emotional distress for a short time
- As methylxanthine beverages as tea and coffee.

Dosage of drugs

b) Psychic and Physical dependence= Addiction:

- Sudden stop of the drug →Withdrawal syndrome → Usually the reverse of the normal pharmacological action.
- As morphine, heroine and barbiturates.

6. Supersensitivity =Intolerance:

- Exaggerated normal action in response to small therapeutic dose of the drug.
- Either due to↓ Elimination of the drug or up-regulation of receptors
- Example: Hyperthyroidism →Supersensitivity to sympathomimetics.
- Decrease the dose of the drug.

7. Hypersensitivity =Allergy:

- Unpredictable abnormal response due to antigen-antibody reaction → ↑ release of histamine, prostaglandins and kinins.
- **Manifested as:**

- Skin reactions: urticaria, rash & edema.
- Fever.
- Asthmatic attack.
- Anaphylactic shock as penicillin.
- Blood dyscrasias as chloramphenicol & sulfonamides.
- Cholestatic jaundice as chlorpromazine.
- Cross allergy between related drugs e.g. Penicillins & Cephalosporins.

Dosage of drugs

8. Idiosyncrasy = pharmacogenetics:

- Abnormal reaction due to genetic abnormality.
- Occurs on first exposure to drugs.
- **Examples**:
  1. Hemolytic anemia in patient with Glucose-6-phosphate dehydrogenase (G6PD) deficiency as primaquine and sulfa drugs.
  2. Malignant hyperthermia with succinylcholine and halothane.

9. Pathological state:

- Some drugs act only in presence of disease:
- Aspirin acts as an antipyretic only in fever
- Digitalis acts as a diuretic only in heart failure

10. Cumulation:

- It occurs when the rate of drug administration exceeds the rate of elimination (by metabolism and excretion).
- e.g. cardiac glycosides especially digitoxin, and guanethidine.
- To avoid cumulation either ↓The dose or ↓ Frequency of administration.

Dosage of drugs

11. Drug-Drug Interactions (Drug Combinations):

- A drug interaction may be classified into:

- **Pharmaceutical interactions:**
  - Some drugs produce insoluble complexes during mixing before administration
  - as succinylcholine (acidic) with thiopentone (alkaline) in one syringe or CaCl2 with cephalosporins in IV infusion.

- **Pharmacokinetic interactions:**

a) Absorption:

- Antacids interfere with the absorption of tetracyclines by forming unabsorbable complexes with It.

b) Distribution:

-a drug may displace other drugs from their plasma protein binding sites → toxicity e.g. salicylates displace warfarin from binding sites → ↑ free warfarin levels → bleeding.

c) Metabolism:

- HME inducers e.g. Phenobarbitone & Phenytoin → ↑Metabolism of other drugs
- HME inhibitors e.g. Estrogen & Cimetidine → ↓ Metabolism of other drugs.

Dosage of drugs

d) Excretion:

- **Reduction in urinary elimination:** **e.g.** Probenecid ↓ renal excretion of penicillin (Increases the duration of action of penicillin).
- **Changes in urinary pH:**

Alkalization of urine (e.g. sodium bicarbonate) ↑ excretion of weak acids

Acidification of urine (e.g. ammonium chloride) ↑ excretion of weak bases.

- **Pharmacodynamics Interactions:** may lead to:

1) Addition =Summation: 1 + 1 = 2

- Use 1/2 dose of each drug.
- Example: Paracetamol + Codeine on analgesic effect.

2) Potentiation: 0+1 > 1

- One drug has no effect. It increases the effect of another effective drug (0+1 > 1).
- As caffeine and Barbiturates (NOT analgesic) potentiate the analgesic effect of Aspirin

3) Synergism: 1 +1 > 2

- ↓Dose of both.
- as rifampicin+ isoniazid in T.B. and penicillin + aminoglycosides in serious infections.

Dosage of drugs

4) Antagonism: 1 + 1 < 2

a) Chemical antagonism:

- As HCl + NaHCO3 or heparin + protamine sulfate.

b) Pharmacological antagonism:

- Two drugs act on the same receptor (agonist and antagonist).
- May be competitive reversible e.g. acetylcholine + atropine, adrenaline + propranolol, or non-competitive antagonism (noradrenaline + phenoxybenzamine).

c) Physiological antagonism:

- Two drugs act on different receptors to give different effect.
- As histamine and adrenaline on bronchi and blood pressure.

Adverse Effects and Toxicity of Drug

❖ Adverse Effects and Toxicity of Drugs

a) <u>Unpredictable adverse effects:</u>

1) Allergy.
2) Idiosyncrasy.

b) <u>Predictable adverse effects:</u>

1) Side effect: The unwanted effects produced by therapeutic dose of drug, e.g. atropine has antispasmodic effect on GIT (therapeutic effect) but cause blurring of vision on the eye (side effect) and atropine causes dry mouth.

2) Secondary effect:

- Bad effect consequent to normal therapeutic action of the drug.
- Example: Oral broad spectrum antibiotics→ ↓Intestinal flora → ↓Vit B & Vit K synthesis and superinfection

3) **Overdose:** e.g. hypoglycemia due to overdose of insulin.

4) **Teratogenicity**:

- Some drugs may produce fetal malformations if they are taken during pregnancy especially in the first trimester.

5) Tolerance, dependence, and addiction.

Adverse Effects and Toxicity of Drug

5**) iatrogenicity**: drug-induced (physician-induced) disease; e.g. aspirin causes peptic ulcer; alpha methyldopa and reserpine cause parkinsonism.

6) **Carcinogenicity**: by tobacco smoking.

7) **Hepatotoxicity:** e.g. by halothane.

8) **Nephrotoxicity:** e.g. by aminoglycosides.

9) **Neurotoxicity**= Nerve damage: e.g. ototoxicity by aminoglycosides and loop diuretics.

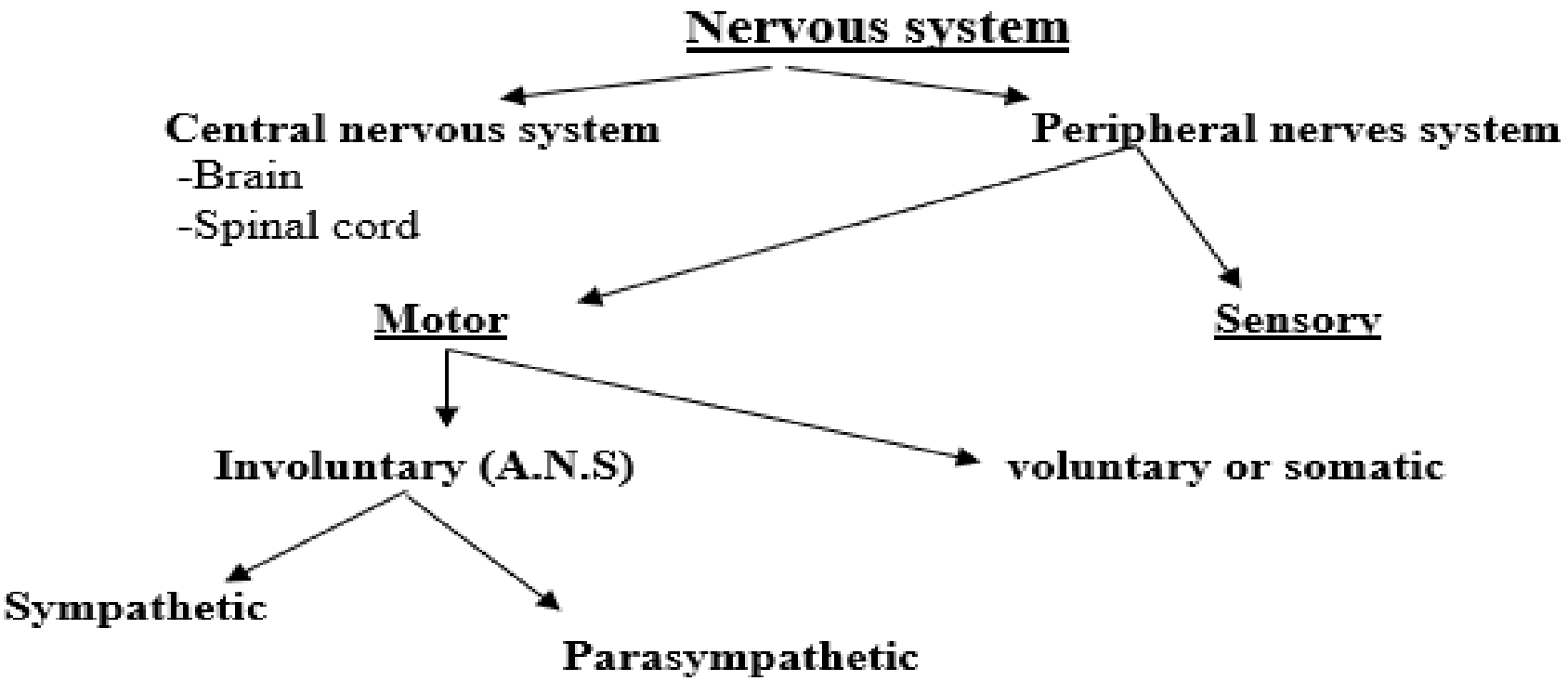
10) Drug interactions.

Autonomic Nervous System (A.N.S.)

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Autonomic Nervous System



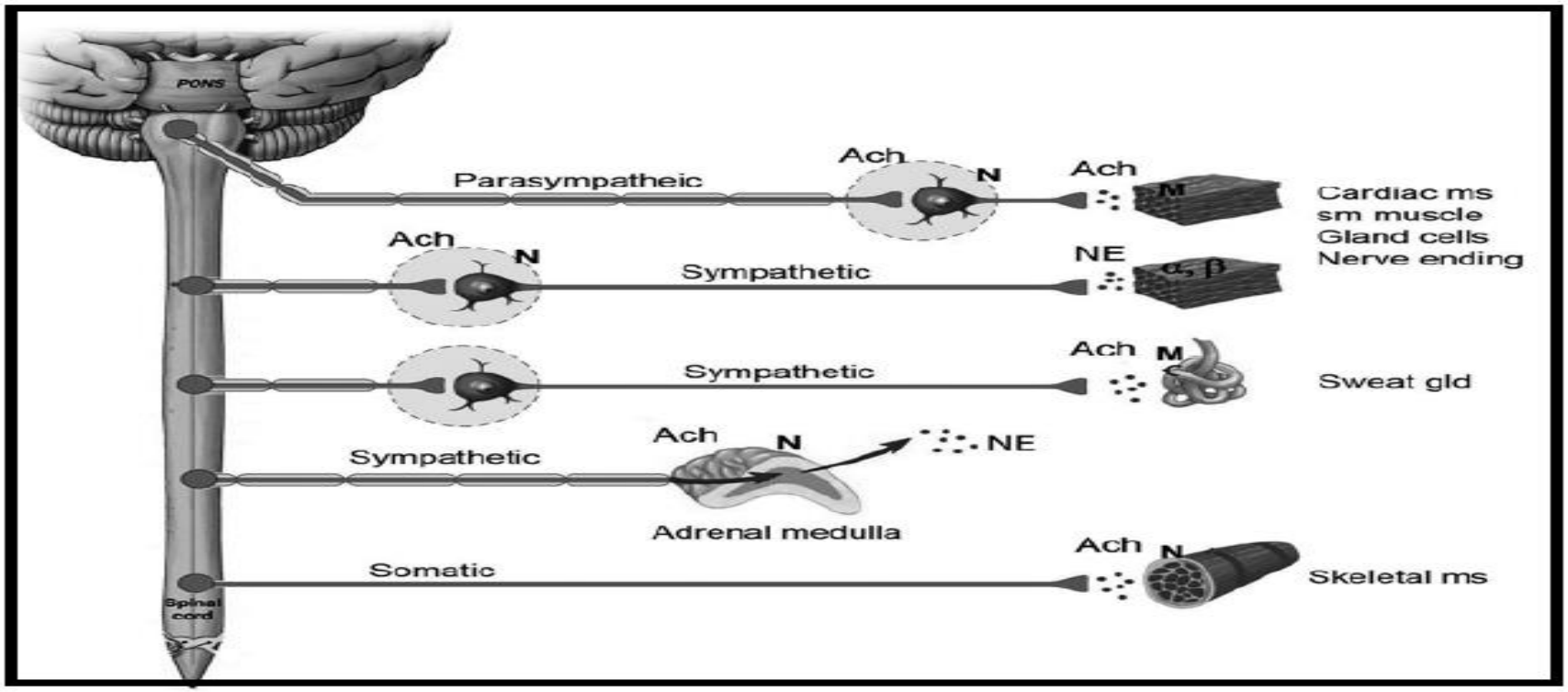
- ANS supply the involuntary muscles (i.e. cardiac muscles and smooth muscles) and exocrine glands
- Communication between nerve cells (and between nerve cells and the effector organs) occurs through the release of chemical substances called mediators or neurotransmitters.

Autonomic Nervous System

- **Autonomic nervous system is divided into: Sympathetic and Parasympathetic**

Sympathetic	Parasympathetic
-It acts during stress: fear-fight-flight-exercise	It acts during rest and digest
-Preganglionic fibres are short	Preganglionic fibres are long
Post ganglionic fibers are long	Post ganglionic fibers are short
Neurotransmitters are norepinephrine (NE) = noradrenaline (NA) in Post-ganglionic fibers and acetyl choline in pre- ganglionic fibers	-Neurotransmitter is acetyl choline (Ach) in pre and post-ganglionic fibers
-Adrenergic receptors: Alpha (α) and Beta (β) receptors. - α-receptors are subdivided into αl and α2, - β-receptors are subdivided into β1, β2, and β3.	- Cholinergic receptors: Muscarinic (M) and Nicotinic (N) receptors. -M- receptors subdivided into Ml, M2, M3, M4, and MS. - nicotinic receptors subdivided into Nn and Nm.
Connected to central nervous system through hypothalamus	

Autonomic Nervous System



❖ Neurotransmitters (Chemical transmitters) in A.N.S.:

- **Acetylcholine**: synthesized, stored and released from specific neurons (fibers) known as Cholinergic neuron.
- **Noradrenaline** (Norepinephrine): synthesized, stored and released from specific Adrenergic neurons.

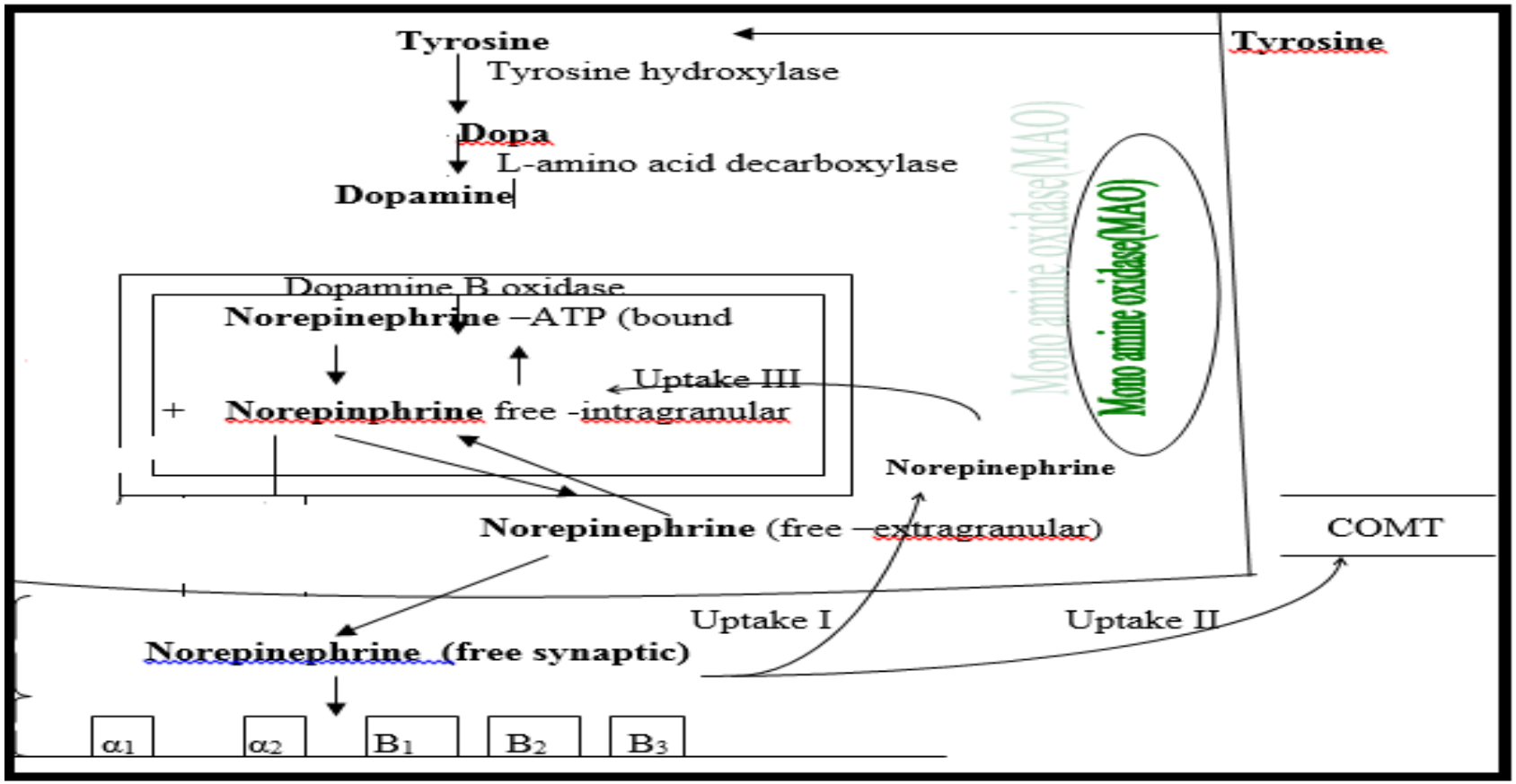
Sympathetic nerves system.

Sympathetic nerves system.

❖ **Adrenergic neurotransmission:** Catecholamine are the major neurotransmitters e.g.

- **Noradrenaline** (Norepinephrine)
- **Dopamine.**

❖ **Synthesis, Storage, Release, and Fate of Norepinephrine:**



A-Synthesis:	**1. Tyrosine is hydroxylated by tyrosine hydroxylase into Dopa.** **2. Dopa is decarboxylated by dopa decarboxylase into dopamine.** **3. Dopamine is uptaken into vesicles and is hydroxylated by dopamine B hydroxylase (oxidase) into noradrenaline.**	**- Inhibited by α-methyldopa & carbidopa**
B-Storage:	• In specific vesicles (in a granular complex) to protect N.E from MAO.	
C-Release:	Depolarization of nerve terminal → ↑ Ca2+ influx →fusion of vesicles with cell membrane → NE release	Inhibited by **guanethidine**
D-NE activity	N.E binds to its receptors (α or β) in organs → response.	
E-Fate & metabolism	**Reuptake:** **1. Most NE → undergoes neuronal reuptake-1, then in neurons:** **- some N.E is inactivated by MAO (metabolism).** **- most N.E → uptake-3 into vesicles (reuptake) and is protected from degradation.**	**- Inhibited by cocaine-tricyclic Antidepressants-guanethidine** **-Inhibited by reserpine.**

Sympathetic nerves system.

E-Fate & metabolism	**2. Little NE undergoes extra-neuronal uptake-2 by effector organs.** **3. Metabolism by cytoplasmic COMT or mitochondrial MAO.** **4. The end product is vanilmandelic acid (VMA) which is excreted in urine.** **5. Excretion in urine unchanged (5%).**	**Inhibited by <u>phenoxybenzamine.</u>** **Inhibited by MAO inhibitors and COMT inhibitors**

Noradrenaline (NA) = Norepinephrine (NE), Mono-amine oxidase enzyme (MAO), Catechol ortho-methyl transferase (COMT).

Sympathetic (Adrenergic) receptors

	α_1 receptors	Presynaptic α_2 receptors	B_2 receptors	B_1 receptors
2nd msngr	Gq (↑ IP3 & ↑ DAG) →↑ Ca2+	Gi (↓ cAMP)	Gs (↑ cAMP)	Gs (↑ cAMP)
CNS	Weak stimulation : Consciousness (alertness, anxiety), mood elevation, motor (anti-fatigue).	Potent inhibition of:	Potent stimulation of:	
Muscles	1. V.C of most blood vessels 2. Contraction of all Sphincters (GIT, urinary). 3. Contraction of dilator Pupillaems (mydriasis) 4. Contraction of uterus 6.Adrenergic sweating (forehead)	1. Presynaptic nerve endings (↓ NA release) 2. Central: ↓ central sympathetic outflow	Smooth muscle relaxation *Bronchi, Uterus *Coronary & skeletal muscle blood vessels	Stimulation of all properties of cardiac muscle
Secretion		<u>Decrease secretion</u> -Norepinephrine -Acetylcholine -Insulin -Aqueous humor -Serotonin <u>Increase secretion</u> Histamine &K^{++}	<u>Increase secretion</u> -Norepinephrine -Acetylcholine -Insulin -Aqueous humor -Serotonin <u>Decrease secretion</u> Histamine &K^{++}	-Increase renin VC &increase aldosterone (Salt and water retention)
Metabolic Actions	Weak stimulation of glycogenolysis and lipolysis	Decrease lipolysis & glycolgenolysis	Potent increase in lipolysis& Glycogenosis	
Selective agonist	Phenylephrine	Clonidine	Salbutamol	Dobutamine
antagonist	Prazosin	Yohimbine	Butoxamine (not used	Atenolol

Drugs affecting sympathetic system

Sympathomimetics :Sympathetic stimulants

Sympatholytics :sympathetic depressants

Adrenergic receptor blocker

-Inhibitors of adrenergic receptors

Adrenergic neuronal blockers

-Inhibitors of synthesis & release or storage of norepinephrine from adrenergic neurons

Direct

They act by stimulation of sympathetic receptors

Indirect

They act by increase release of norepinephrine

-Amphetamine ,

Dual

They act by stimulation of sympathetic receptor and norepinephrine release

-Ephedrine , pseudoephedrine

Specific :Stimulate one receptor

-**Phenylephrine** :α_1 stimulant

-**Dobutamine**:β_1 stimulant

-**Salbutamol**: β_2 stimulant

Non specific stimulate more than one receptor

-**Norepinephrine** :$\alpha_1=\alpha_2=\beta_1>\beta_2$

-**Epinephrine**:$\alpha_1=\alpha_2=\beta_1=\beta_2$

-**Isoprenaline**:$\beta_1=\beta_2$

-**Dopamine**: $D_1> \beta_1>\alpha_1$

NB: Yohimbine: is a sympathomimetic that acts by blockade of α_2 inhibitory receptors.

Sympathetic nerves system.

- Classification of sympathomimetic according to the chemical structure

Catecholamines	Non-Catecholamines
Contain catechol ring. (similar chemical structures)	Not contain catechol ring.
Rapid onset with short duration of action.	Longer duration of action.
Metabolized by MAO (Mono-Amino Oxidase) intraneuronally and by COMT (Catechol O-methyltransferase) in the synaptic space.	Less degradation by MAO or COMT.
Not administrated orally. (not stable)	Can be administrated orally. (stable)
Weak penetration for BBB.	Good penetration for BBB.
They are:- Adrenaline, noradrenaline, isoprenaline, dopamine and dobutamine	As: Clonidine, terbutaline and amphetamine.

Sympathetic nerves system.

1-Direct non-specific sympathomimetic

1. Adrenaline (Epinephrine): $\alpha_1 = \alpha_2 = B_1 = B2$ agonist

- **Chemical structure**: catecholamine, Short duration of action, Ineffective orally
- Given (IV, IM and SC), intracardiac, poor passage across B.B.B,
- Metabolized by COMT or MAO into VMA which is excreted in urine

❖ **Mechanism of action:** stimulates $\alpha_1 = \alpha_2 = B_1 = B2$

❖ **Pharmacological actions:**

1. Heart: stimulates cardiac B1-receptors leading to:

- +ve Inotropic (↑ Contractility)
- +ve Chronotropic (↑ Heart rate) → **Tachycardia.**
- +ve Dromotropic (↑ A-V conduction)
- ↑ Cardiac work → ↑ Oxygen needs → **angina pectoris**
- ↑ Excitability & Automaticity→ **arrhythmia**
- ↑ ALL Cardiac properties→ ↑ C.O.P.

2. Blood vessels (BV):

- Vasoconstriction (skin, mucous membrane and viscera) → ↑ blood pressure. (α1)
- Vasodilatation of coronary blood vessels and skeletal muscles. (β2)

Sympathetic nerves system.

3. Blood pressure:
- ↑ systolic (β1-stimulation &↑ COP). ,
- No effect on diastolic due to balanced effect on α1 mediated VC and β2 mediated VD

4. **Relax of bronchial smooth muscles** → bronchodilatation. (β2)
5. ↓ Gut motility and urinary retention. (α1 and β2)
6. Mydriasis. (α1) & Relaxation of uterus. (β2)
7. ↑ Blood glucose. (β2 and α2) & ↑ Lipolysis and fatty acid concentration (B1).
8. **Skeletal muscles**: Tremors (B2). ↑ K+ uptake leading to hypokalemia, anti-fatigue action
9. Anti-histamine and anti-allergic action (Physiological antagonist of histamine) → on blood vessels, B.P., and bronchi.).

❖ Therapeutic Uses:

1- Anaphylactic shock IM
2- cardiac arrest (IV or intracardiac)
3- Acute bronchial asthma (Replaced by selective β2-agonists)
4- Hypoglycemia & hypotension
6- With local anesthetics. (vasoconstriction → ↓ absorption → prolong the duration of action)
7- To stop bleeding as in cases of epistaxis except in hypertensive patients (Adrenaline is given locally as nasal pack).

Sympathetic nerves system.

❖ Adverse Effects (side effects):

- Angina (increase cardiac work)
- Tachycardia & arrhythmia
- Hypertension (may lead to cerebral hemorrhage).
- Hyperglycemia

❖ Contraindications:

- Hypertension.
- Coronary heart diseases. (as angina)
- Diabetes.
- Tachyarrhythmia.

Sympathetic nerves system.

2. Noradrenaline (Norepinephrine): α1= α2 = B1 agonist (weak on B2)

- Naturally **catecholamine**
- Administered by I. V. Infusion only due to strong vasoconstriction → necrosis of tissues.
- Acts as adrenaline but affect mainly on α receptors (α1= α2= B1 receptors with little or no effect on B2 receptors.

- **Actions:** ↑ cardiac-stimulant effect (β1) → ↑ systolic blood pressure & VC of all blood vessels (α1) → ↑ diastolic blood pressure (T. P.R). → ↑ A.B.P. → "reflex bradycardia".

- **Therapeutic uses:** Treatment of cardiogenic shock and in acute hypotensive states.

- **Side effects:** Severe hypertension (cerebral hemorrhage), reflex bradycardia, Gangrene if injected in small vessel, Abortion in pregnant women

3. Isoprenaline: B_1=B2 agonist

- Synthetic catecholamine, Long duration of action.
- Given sublingually, parenterally and by inhalation. metabolized by COMT not MAO.

- **Actions:** ↑ Contractility and heart rate (β1) & VD of skeletal and coronary vessels. (β2) → ↑ systolic (β1) and ↓ Diastolic(β2) & Bronchodilatation (β2), Uterine relaxation (β2)

- **Therapeutic uses:** Acute bronchial asthma. (Replaced by β2-agonists due to side effects). & bradycardia, heart block, premature labor & in peripheral vascular diseases

- **Side effects:** Tachycardia & cardiac arrhythmia & palpitation, Skin flushing

4. Dopamine: $D_1 > \beta_1 > \alpha_1$ agonist

- Natural catecholamine present in CNS and peripherally.
- Short duration of action, Given only by IV infusion, Metabolized by COMT and MAO.

- **Actions:**
  - **At low dose:** Acting on D1 receptors → VD → ↑ renal blood flow.
  - **At moderate dose:** Acting on β1 receptors → +ve inotropic & chronotropic effects.
  - **At high dose**: Acting on α1 receptors → VC → ↑ blood pressure.

- **Therapeutic uses:** cardiogenic shock (↑ rate and force of heart contractions with renal VD → ↑ renal blood flow) & in acute renal failure & acute heart failure & hypotension

- **Side effects:** Tachycardia, arrhythmia, hypertension & nausea.

Sympathetic nerves system.

Specific sympathomimetic: They stimulate one receptor

1. β1 receptor-agonists:

- **Dobutamine:** Catecholamine, given intravenous drip. Metabolized by COMT mainly.
- Prenalterol: non-catecholamine, given orally & parenterally. long acting

- Direct selective B1 agonist.
- It is a potent inotropic action (cardiac contractility) more than chronotropic (heart rate) → ↑ COP.
- **Uses:** Heart block and congestive heart failure, Better than dopamine (no effect on D1 or α1 receptors). & in Cardiogenic shock.

- **Adverse effects:** High dose → tachycardia, arrhythmia and angina.
  - Prolonged use → tolerance due to downregulation of B1 receptors

2. B2 receptor - agonist

❖ **Preparations:** Non-catecholamine

1. Short acting (t½ about 4-6 hours, Rapid onset of action:

EX - Albuterol & Salbutamol (Ventolin)®: Taken orally, parenterally and by inhalation.

- Terbutaline: Used orally & inhalation. More selective action and less side effects than salbutamol
- Ritodrine: given IV or orally. Used mainly to prevent premature labor.

Sympathetic nerves system.

2- **Long acting**: (t½ about 12 hours, Slow onset of action

Ex: Salmeterol & Formoterol: Given only by inhalation for prophylaxis of bronchial asthma.

- **Pharmacological actions:**

- β2 receptors agonist → relaxation of bronchial and uterine smooth muscles, and VD.
- Promote hepatic glycogenolysis and uptake of K+ into the cells.

- **Therapeutic uses:**

- **Bronchial asthma**: given orally, parenterally, and more commonly by inhalation (salbutamol & terbutaline in acute attacks, salmeterol & formoterol in prophylaxis).
- **Prevent premature labor** (ritodrine is commonly used).

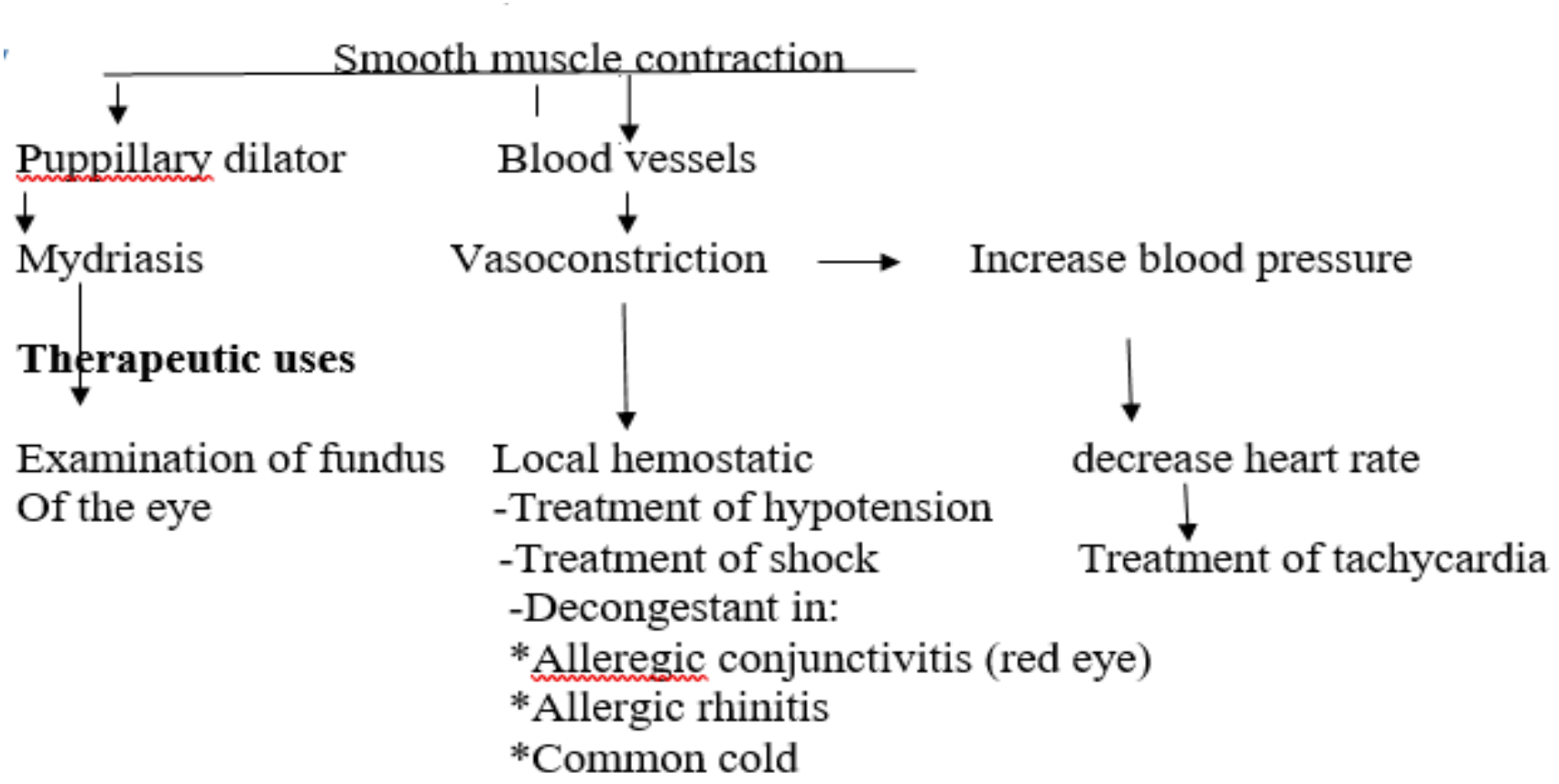
- **Adverse effects:**

- Tolerance (loss of action after long time)
- Hypotension & tachycardia .
- Hyperglycemia & Tremors due to increase glycogenolysis and blood flow to muscles
- Hypokalemia is due to shift of K+ into cells

Sympathetic nerves system.

3. α1 – receptor agonists

- Non catecholamine, administrated orally, intravenous or topical (nasal or eye drops).



❖ **Side effects:** Long term use of Nasal drops Atrophy of mucous membrane , loss of smell (anosmia) & Hypertension

Sympathetic nerves system.

❖ Preparation of α1 – receptor agonists :

- Phenylephrine, Methoxamine: used in: hypotensive states (parenterally)
- Phenylephrine is also used as a mydriatic (eye drops), and a nasal decongestant (oral & nasal drops).
- Midodrine: given orally in chronic postural (orthostatic) hypotension.
- Xylometazoline, oxymetazoline Naphazoline: as nasal decongestant in allergic rhinitis, colds, and sinusitis. (nasal drops or sprays). Also given as eye drops in allergic inflammation.

Indirect sympathomimetic: Increase norepinephrine release

➢ Amphetamine

- Non catecholamine, Basic drug, Rapid onset, potent , short action. potent CNS-stimulant effect, Given (Orally, IM and IV).

❖ Action:

- Acting indirectly → ↑ release of NE and dopamine and prevent reuptake.
- **Centrally**:
  - Euphoria, wakefulness, alertness, and anti-fatigue, ↑ mental and physical activity), These actions are followed by fatigue and dysphoria.
  - insomnia, ↓ Appetite. (Anorexigenic effect) - Analgesic effect.
  - Tolerance and physical dependence (addiction) occur on prolonged use

Sympathetic nerves system.

- **Peripherally:** - Hypertension & reflex bradycardia. - Bronchodilation
  - Constipation due to contraction of GIT sphincters as a result of α1 stimulation
  - Urinary retention due to contraction of UT sphincters (α1 stimulation) & active mydriasis.

N.B.: Amphetamine causes sedation in children.

❖ **Therapeutic uses:** (Amphetamine is not commonly used nowadays)
- Narcolepsy (day time sleep)
- Obesity (appetite suppression)
-Attention Deficit Hyperkinetic Disorders in children (ADHD) (Methylphenidate is preferred)
- Treatment of nocturnal enuresis

❖ **Adverse effects** are loss of appetite and insomnia. Hypertension. Urinary retention Constipation, Tolerance and addiction (=chronic toxicity).

- Methamphetamine: very potent CNS stimulant with weak sympathomimetic actions
- Methylphenidate and Modafinil: used in treatment of ADHD.

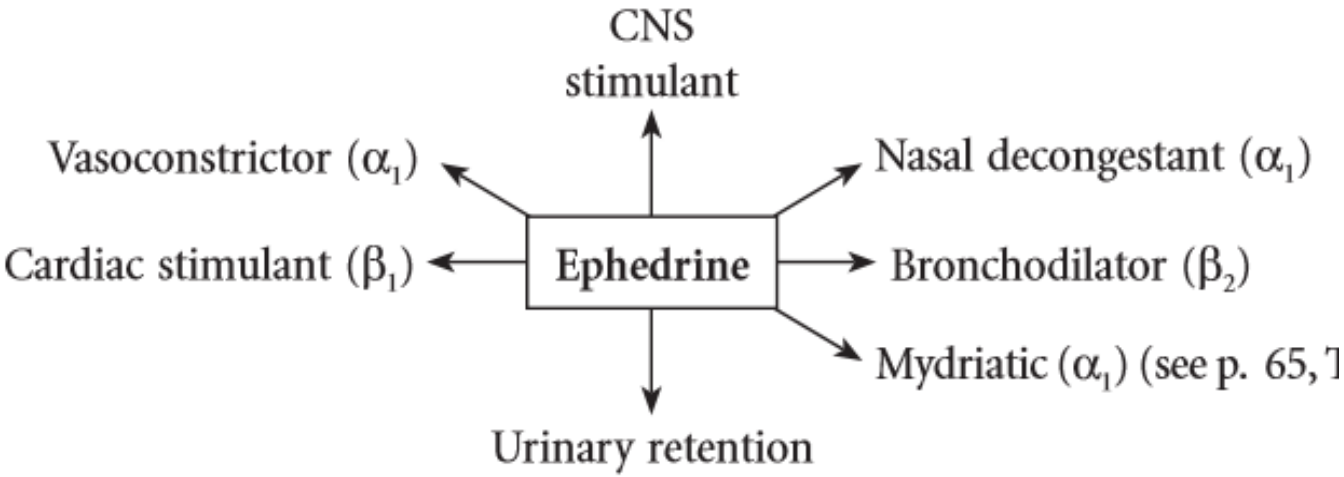
Treatment of amphetamine toxicity:
- Acidification of urine by ammonium chloride or vitamin C.
- CNS inhibitors as barbiturates or benzodiazepines.
- Anti-hypertensive agents

Sympathetic nerves system.

Mixed acting sympathomimetics

- Ephedrine, pseudoephedrine

- Stimulate α and β receptors directly and indirectly by increase releasing of noradrenalin from its stores.
- Non catecholamine, Alkaloids. Slow & prolonged duration. -Mild CNS-stimulant effect
- Given (Orally, IM and S.C. drops (eye & nasal).
- **action :** similar to amphetamine with more bronchodilator effect



Sympathetic nerves system.

❖ **Therapeutic uses:**

1. Treatment of common cold , they reduce nasal congestion and sputum formation (Pseudoephedrine is better).
2. Treatment of chronic bronchial asthma
3. Drug of choice for Treatment of hypotension during spinal anesthesia
4. Mydriatic eye drops 1-3%

❖ **Side effects:** insomnia, hypertension, tachycardia, palpitation, difficulty in urination; tachyphylaxis occurs on repeated administration

❖ **Contraindications:** As adrenaline (hypertension, thyrotoxicosis, arrhythmia, angina) + prostatic hypertrophy in old males.

Pseudoephedrine: has less CNS and CVS side effects and used mainly as nasal decongestant

Autonomic Nervous System (A.N.S.)

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Sympatholytic =Drugs that depress sympathetic system

Sympathetic receptor depressants

α blockers

β receptor blocker

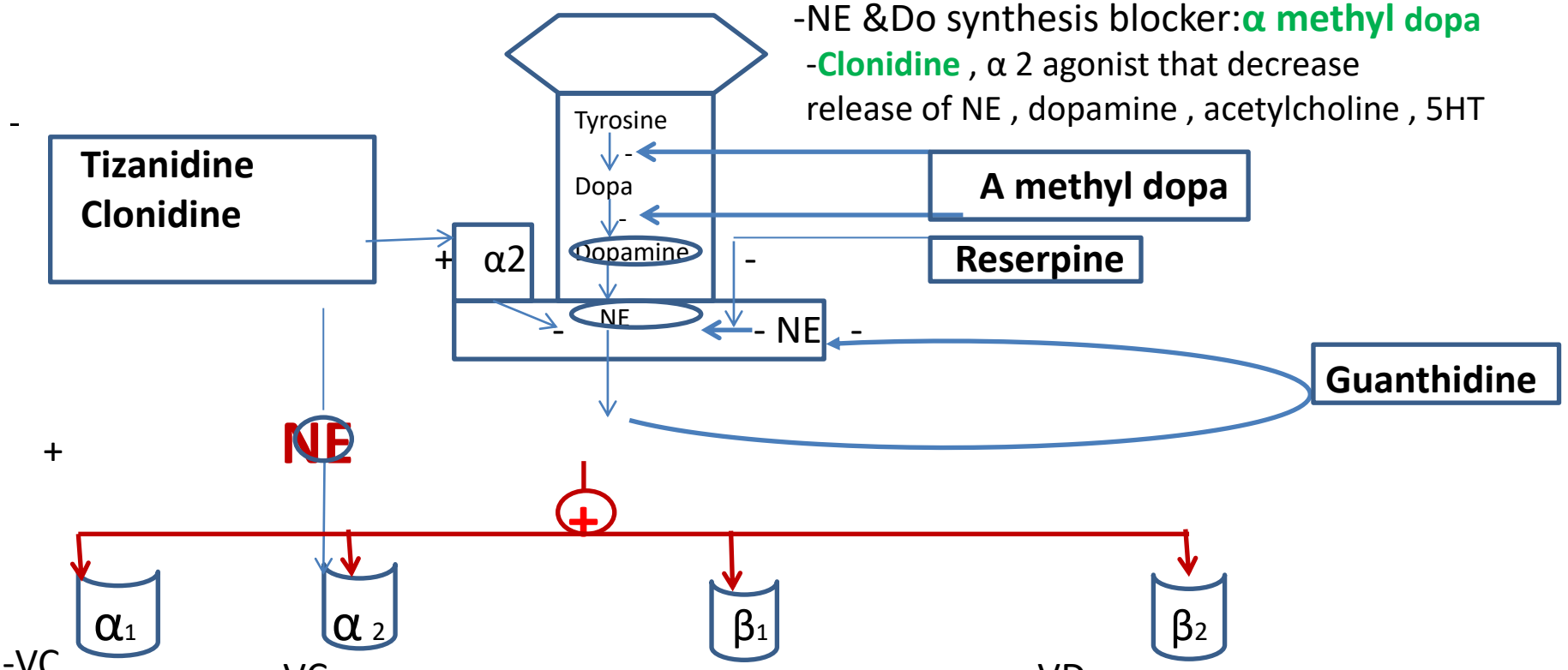
Adrenergic neuronal blockers

-Uptake 1 blocker : **guanethidine**

-Uptake 3 blockers : **reserpine**

-NE &Do synthesis blocker:**α methyl dopa**

-**Clonidine** , α 2 agonist that decrease release of NE , dopamine , acetylcholine , 5HT



-VC
-Mild glycogenolysis & lipolysis

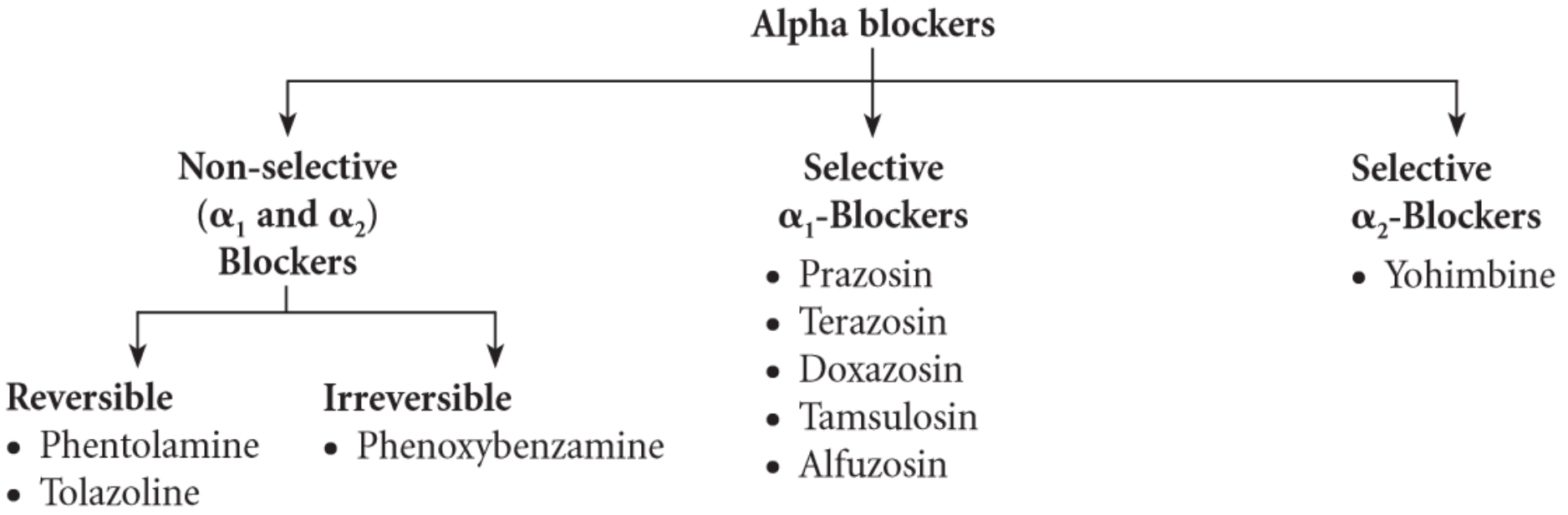
-VC
Inhibition of salivation

-Cardiac stimulation
-Increase renin (VC)

-VD
-Lipolysis& glycogenolysis
-Increase NE &aqueous & insulin

Sympatholytic

➢ α-blockers:



1- Non-selective α-blocker:

1. **Phenoxybenzamine :**. Irreversible non-competitive blocker (α1 & α2) with long action.

2. **Phentolamine** .: Reversible competitive blocker (α1 & α2) with short action.

Sympatholytic

❖ Action:

- Vasodilatation and decrease peripheral resistance. urinary bladder relaxation (block α1)
- Increased release of NA from the adrenergic nerve endings (block α2 receptors) → cardiac stimulation and produce tachycardia, palpitation, cardiac arrhythmias, etc.

❖ Therapeutic uses:

1. In hypertension associated with pheochromocytoma (phenoxybenzamine is better). in combination with B blockers
2. In peripheral vascular diseases (P.V.D).
3. In benign prostatic hypertrophy (BPH). (Tamsulosin is better).

❖ Adverse effects:

- Postural hypotension, Tachycardia, arrhythmia, and anginal pains
- Nasal congestion. Sexual dysfunction (Failure of ejaculation and impotence)

Sympatholytic

2. Selective α1-Blockers:

- Prazosin (short acting), Terazosin (long acting),
- Tamsulosin (Omnic)® specific on urinary bladder

❖ Pharmacological actions:

- V.D. of both arteries (afterload) and veins (↓venous return= preload), and ↓ arterial blood pressure (A.B.P.)
- No tachycardia.
- Potent relaxation of UT &GIT sphincters.

❖ Therapeutic uses:

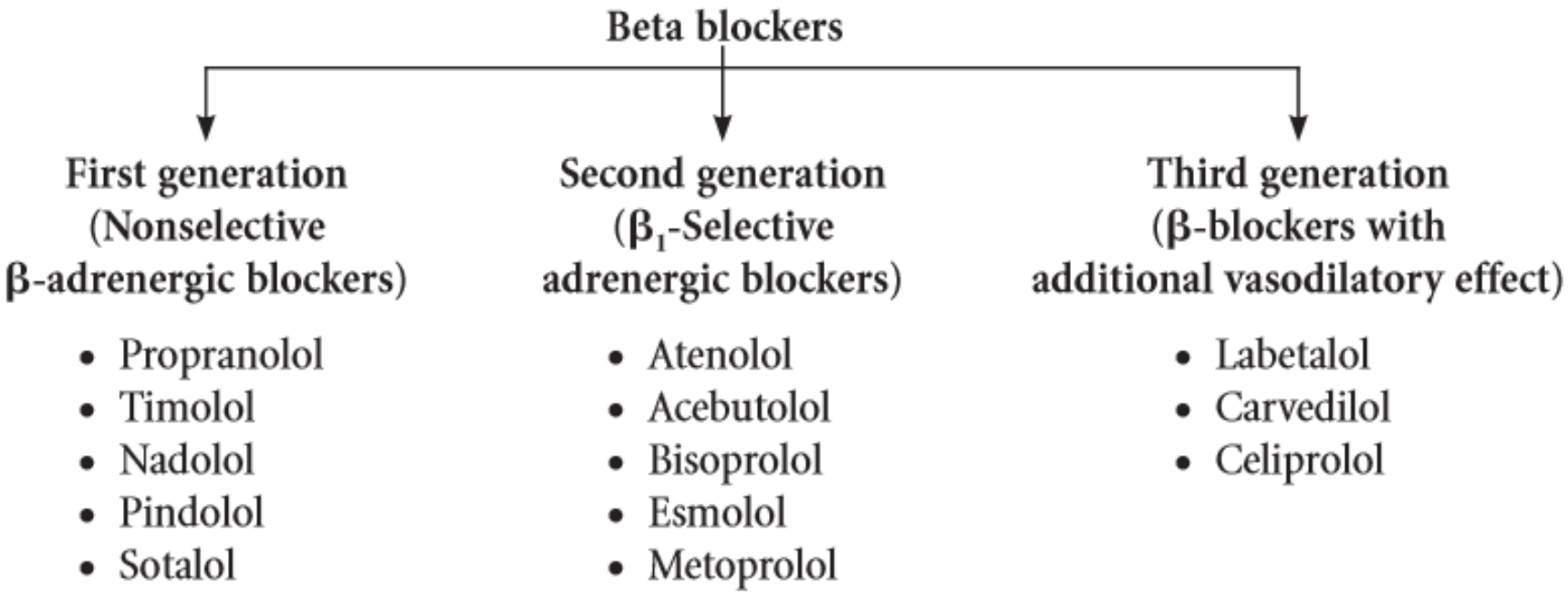
1. Hypertension associated with P.V.D., congestive heart failure.
2. Mild-to-moderate hypertension (better adds Diuretic+ B-Blocker)
3. Secondary hypertension due to pheochromocytoma.
4. BPH. (Tamsulosin is more selective).

❖ Adverse effects:

1. **First dose effect**: Postural hypotension after first dose. (prevented by start with a small dose at bed time), then the dose is gradually increased.
2. Nasal congestion.
3. Na+ and water retention due to decreased RBF, corrected by adding a diuretic.

Sympatholytic

- **Beta-adrenergic antagonists (B- blockers)**



Sympatholytic

❖ **Pharmacokinetics = Lipid Solubility:**

	Lipophilic B blockers	Hydrophilic B blockers
Examples:	Propranolol-Pindolol-Timolol-Bisoprolol-Metoprolol	Nadolol-Atenolol-Sotalol.
1-Absorption:	Well absorbed orally.	Incomplete (poor-delayed) oral absorption
2-Distribution:	Passes easily B.B.B. marked CNS actions	Poorly penetrates B.B.B. weak CNS actions.
3-Plasma protein binding:	Highly bound to plasma proteins → drug interaction	Less
4-Metabolism:	Extensive hepatic metabolism by (HME) → drug interaction	Mainly excreted slowly unchanged in urine
5-Excretion:	Biliary	Renal
6-Duration of action	Short due to extensive hepatic metabolism, requires frequent daily doses	Long due to poor hepatic metabolism, given as single daily dose

Sympatholytic

❖ Pharmacodynamics:

- **Block β1 receptors on the heart** → -ve inotropic, chronotropic and dromotropic action**.** **(**Useful in Atrial tachyarrhythmia) → ↓COP & Cardiac work &↓ O2 needs (Useful in Angina)
- **Block β1 receptors on kidney** → ↓ renin release
- ↓ blood pressure due to B1 blockade (↓COP cardiac & decrease renin)

- **Block β2 receptors on**:
  - **Smooth muscle contraction:** Vasoconstriction (↓ blood flow to most organs), Bronchoconstriction & Uterine contraction
  - **Metabolic effects:** ↓ Glycogenolysis, Lipolysis,
  - **Decrease release**: NE &Ach &5HT (Migraine prophylaxis) & insulin &aqueous humor formation (↓ IOP)
  - **Skeletal muscle:** → skeletal muscle weakness and tiredness (↓↓tremors)
  - **CNS inhibition**: Sedation & antianxiety, Motor depression

❖ Therapeutic uses:

1. **Hypertension.** especially in patients with angina, or cardiac arrhythmias.
2. **Angina pectoris**: for all types of angina except vasospastic angina.
3. **Cardiac arrhythmia** (atrial arrhythmias). Acute arrhythmia during surgery (i.v. esmolol).
4. **Early mild heart failure**. (carvedilol, metoprolol and bisoprolol)

Sympatholytic

5. Treatment of **essential tremors**
6. **Anxiety** and panic disorders.
7. **Glaucoma** → ↓ aqueous humor formation. (Timolol as eye drops)
8. **Migraine**. (as prophylactic)
9. **Hyperthyroidism**

❖ Adverse effects

- Bradycardia, heart block, Heart failure & Hypotension
- Bronchospasm, Cold extremities, and fatigue
- CNS depression, sedation. and sleep disturbances
- Silent hypoglycemia due to decrease glycogenolysis. → mask the warning signs and symptoms of hypoglycemia (tachycardia &anxiety)
- Withdrawal symptoms: Sudden stoppage of B blockade cause rebound hypertension tachycardia, arrhythmia, and anginal pain especially in patients with ischemic heart diseases due to upregulation of B receptors.

Sympatholytic

❖ Contraindications:

1. Bradycardia & Hypotension.
2. Bronchial asthma & PVD as Raynaud's disease.
3. Variant or vasospastic angina.
4. Diabetes mellitus.
5. Severe heart failure.
6. Never Stop B-blockers Suddenly.

❖ Drug Interactions of B-b1ockers:

1) Lipophilic B-blockers are highly bound to plasma proteins → displace other drugs as digitalis → “digitalis toxicity".
2) B-blockers → ↓Hepatic blood flow→ ↓ Metabolism of lidocaine & their own
3) B-blocker + digitalis → severe bradycardia and AV block.
4) B-blocker + verapamil or diltiazem → severe bradycardia and AV block.
5) Insulin/sulfonylureas × B-blockers: Nonselective B-blockers inhibit glycogenolysis and delay recovery from hypoglycemia.

Sympatholytic

1. **Non-selective B-blockers= First generation:** (block B1- and B2 receptor) as Propranolol and Timolol

2. **Cardioselectivity B-blockers= Selective B1-blockers= Second generation:**

   - as Atenolol, Metoprolol, Bisoprolol, and Esmolol.
   - They block B1-receptors (but in large doses, they can block B2 receptors)
   - Used mainly in treatment hypertension, angina and arrhythmia.
   - Advantages: Allowed in variant angina, in P.V.D, in bronchial asthma, D.M

3. B-Blockers with additional Vasodilator = Third generation:

   - as Labetalol & Carvedilol
   - They block B1, B2, and α1- receptors

4. β blockers with intrinsic sympathomimetic activity (I.S.A.) = Partial β agonists

   - As Pindolol, acebutolol, & labetalol.
   - They have less side effects (bradycardia, hypotension, hypoglycemia) because they act as β agonists in large dose
   - preferred in treatment of hypertension,
   - Contraindicated in treatment of angina patient because they may increase cardiac work and heart rate

5. Membrane stabilizing activity (MSA):

- As Propranolol
- They have membrane-stabilizing activity by sodium channel blockade (local anaesthetic activity) → preferred as antiarrhythmic

➢ B-and α-Blockers:

1. Labetalol:

- Blocks B- and α1,-receptors in a ratio of 3:1.
- Less potent than propranolol as B-blocker, and less potent than phentolamine as α-blocker.
- Decreases ABP by decreasing both COP and TPR.
- It causes V.D. and hypotension without reflex tachycardia.

❑ **Used in:**

1. Essential hypertension, including emergency hypertension and pregnancy -induced hypertension.
2. Pheochromocytoma (it is used alone).

2. Carvedilol: .

- As labetalol: B and α, blocker+ Antioxidant.
- It is used in treatment of heart failure and hypertension

Autonomic Nervous System (A.N.S.)

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Sympatholytic

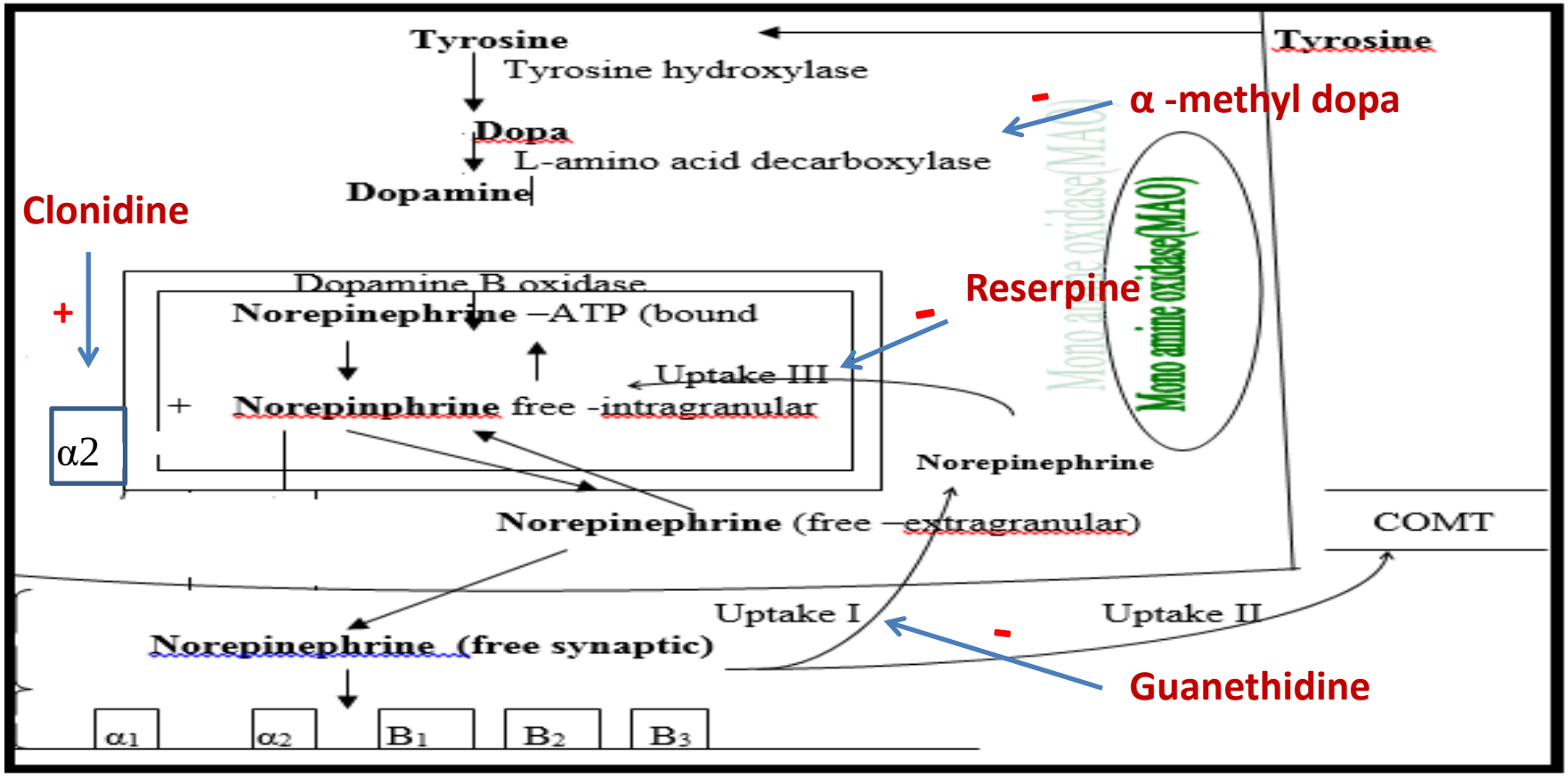
Adrenergic neuronal blockers

-Uptake 1 blocker : guanethidine

-Uptake 3 blockers : reserpine

-NE &Do synthesis blocker:α methyl dopa

- α 2 agonist that decreas release of NE , dopamine , acetylcholine , 5HT: Clonidine



Sympatholytic

❖ Adrenergic neuronal blockers

- They act by inhibition of synthesis (α methyl dopa) , storage (reserpine) or release (guanethidine) of norepinephrine in sympathetic neurons..

	Guanethidine	Clonidine	Reserpine	α methyl dopa
Mechanism of action	Inhibition of uptake I from cytoplasm to nerve terminal	Decrease NE release by stimulation of α_2 receptors	Inhibition of NE storage by blocking intra-granular uptake III due to destruction of storage vesicles	Inhibition of NE synthesis by inhibition of L amino acid oxidase enzyme
Pharmacokinetics:	-Poorly absorbed orally. Given also eye drops -Can not Passes B.B.B -Slowly excreted in urine	-Well absorbed orally. -Passes B.B.B. -Partly metabolized and partly excreted unchanged in urine.	-Well absorbed orally. Given also IV and IM -Passes B.B.B -Excreted in urine	-Given orally -Passes B.B.B. -Excretion: inactive metabolites are excreted in urine.
Blood vessels	Initial vasoconstriction due to ↑ NE in synaptic ↑ postsynaptic α_2 receptors -Long acting vasodilatation due to ↓ NE release ↑ presynaptic α_2		Slow vasodilatation due to ↓ NE synthesis ↓ NE synthesis Metabolized to α methyl NE Which ↑ α_2 receptors	
Heart	**Initial tachycardia due to ↑ NE in synaptic cleft**	**Bradycardia due to decrease NE release**	**Bradycardia due to ↑ Parasympathetic ↓ sympathetic &**	

	Guanethidine	Clonidine	Reserpine	α methyl dopa
CNS	No effect Not pass BBB	-CNS depression -Sedation, analgesia due to imidazole receptors	Inhibition of dopamine release leading to * gynecomastia & infertility due to increase prolactinoma *Depression and sedation *Increase muscle tone (parkinsonism)	
Eye	Miosis and decrease intraocular pressure			
GIT	Diarrhea & ↑ motility due to para-sympathetic	Inhibition due to decrease acetylcholine release	Diarrhea & increase motility due to para-sympathetic	
Therapeutic uses	1-Long term treatment of hypertension 2-Eye drops in treatment of glaucoma (apraclonidine) -Analgesic -Preanesthetic Medication -Antidiarrhea -Sedative in withdrawal of addictive drugs		1- Emergency and long term treatment Of hypertension 2-Antipsychotic	1-Long term treatment of hypertension especially during pregnancy
Side effects	- Bradycardia, diarrhea, peptic ulcer, bronchospasm, sedation , - salt and water retention → tolerance & weight gain , Postural hypotension (the least with α methyl dopa). - reserpine and α methyl dopa causes parkinsonism & infertility, gynecomastia &hyperprolactinemia			
Contraindications	Heart failure (cardiac depressant) ,bronchial asthma , peptic ulcer (bronchospasm and increase HCl secretion due to parasympathetic predominance) , pheochromocytoma (do not affect epinephrine release from adrenal gland).			

Drugs affecting the Parasympathetic system (cholinergic)

Parasympathetic nerves system

Parasympathetic nerves system (cholinergic)

❖ **Cholinergic neurotransmission:**
- Acetylcholine (Ach) is the neurotransmit of Parasympathetic system.

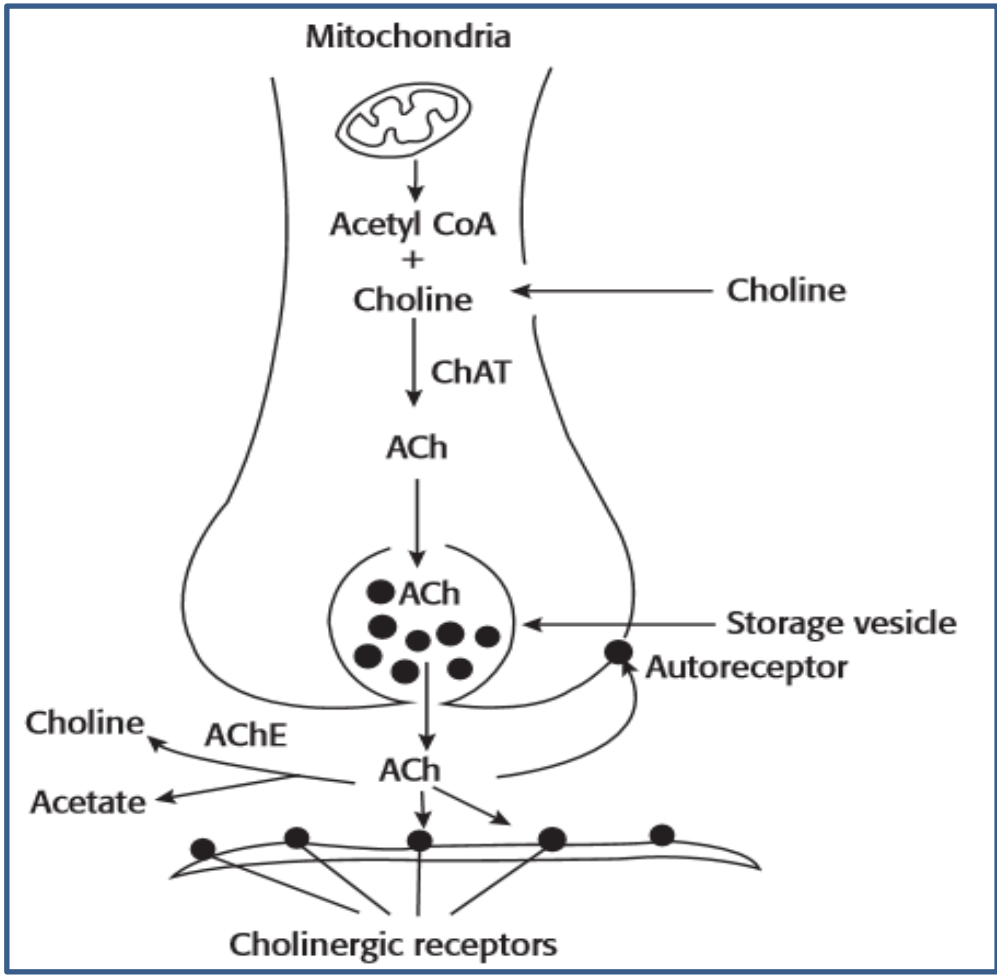
❑ **Receptor binding:** ACh can bind to 2 types of receptors:

- Muscarinic receptors (M) in the involuntary smooth muscles & glands

  -There are 5 subgroups of muscarinic receptors: M1-M5

- Nicotinic receptors:
  -Neuronal(Nn): in autonomic ganglia.

  - Muscle(Nm) in the skeletal muscles



Synthesis, storage and fate of the released ACh at the cholinergic nerve endings.
- ChAT, choline acetyltransferase
- AChE, acetylcholinesterase

Parasympathetic nerves system

- **Metabolism of ACh actions:**
  - ACh is metabolized by acetylcholine-esterase (AChE) (Cholinesterase enzyme) → choline + acetate

- **NB: Cholinesterase has 2 types**

True cholinesterase (True (specific) Acetylcholine-esterase (AChE)	**Pseudo-cholineesterase (Pseudo (nonspecific) Butyrylcholine-esterase (BChE)**
Specific for ACh	Non specific
It is present in cholinergic nerve terminals, nervous tissue and ganglia, RBCs	It is present in plasma, liver, skin, CNS
It is slowly synthesized. It takes 120 days for regeneration (3-6 Months) .	It is rapidly synthesized in the liver (2-3 Weeks)
Breaks: - Endogenous Ach - Methacholine (Parasympathomimetic)	Breaks other choline derivatives (drugs like succinylcholine, butyryl choline, benzyl choline. but it does not hydrolyze methacholine.

	Muscarinic receptors			Nicotinic receptors	
	M1	M2 &M4	M3	Nn (neuronal)	Nm (muscle)
Location	CNS, Stomach	Heart	Glands, Eye, GIT wall	Ganglia, CNS	NMJ
C.N. S	-Stimulation of memory, vomiting, respiratory - ↑ muscle tone			Stimulation of all autonomic ganglia	
Muscles		-↓ heart rate &↓ atrial contractility, automaticity &excitability -↑ atrial conduction -no effect on ventricular contraction	- Contraction of wall of GIT, UT, bronchi, uterus, blood vessels (weak). - Eye: → miosis. - Nitric oxide potent vasodilator		NMJ → skeletal muscle contraction
Secretions	- ↑ Gastric HCl secretions		- ↑↑ all body secretions (sweating, salivation, lacrimation, etc). - ↑ aqueous drainage - ↓intraocular pressure	- ↑ release of most of transmitters -↑adrenaline release from suprarenal gland	
Non-Selective agonist	Acetylcholine				
Selective antagonist	Pyrenzepine	Gallamine	……..	Trimetaphan	d-tubocurarine
Non-selective antagonist	Atropine				

Parasympathetic nerves system

Drugs affecting parasympathetic system

Parasympathomimetic
parasympathetic stimulants

Parasympatholytic
Parasympathetic blockers

-They all contain amine group to be similar to acetyl choline (natural parasympathetic neurotransmitter which contain quaternary amine nitrogen group.

	Tertiary amine drugs	Quaternary amine drugs
Electric charge	Non- Charged	charged
Solubility	More lipophilic	Less lipophilic
Absorption from GIT	Rapid	Slow
Passage through blood brain barrier (BBB) and aqueous barrier	Rapid	No
Effect on CNS	High	Low
Affinity for cholinergic receptors & cholinesterase enzyme	Low (Less than endogenous neurotransmitter acetylcholine because nitrogen atom is uncharged	High (More similar to endogenous neurotransmitter acetylcholine due to charged nitrogen atom

Parasympathomimetic

Parasympathomimetics

Drugs that stimulation of parasympathetic nervous system

Direct acting
Receptor stimulants

Choline esters
- Methacholine
- Carbachole
- Bethanechol
- Acetyl choline

Natural plant Alkaloids
- Pilocarpine
- Muscarine (not used as a drug)

Indirect acting (Anticholine esterase)
(↓ ChEs → ↑ ACh → ↑ M & N)

Reversible

Short acting
-Edrophonium

Intermediate acting

Teriary amines
Physiostigmine

Quaterary amines
Neostigmine
Pyridostigmine
Ambenonium

Irreversible
-Organophosphorus compounds

-
-

Parasympathomimetic

- **ACh** is not used clinically because:
  it has very short duration of action (rapid hydrolysis by ChE enzyme),
  - it lacks selectivity.
- Cholinomimetic drugs are drugs that produce effects similar to ACh or cholinergic nerve stimulation, but with more selectivity and fewer side effects than ACh.
- Antidote is atropine

❖ Pharmacological actions:

❑ On Muscarinic receptors:

- **CVS** (M2): Bradycardia, ↓ heart rate &↓ atrial contractility and Hypotension
- **Smooth muscles (M3):** Contraction → Bronchospasm, bladder wall & GIT motility → micturition, defecation
- **Eye (M3 :** Miosis, ↓ intraocular pressure (IOP) in glaucoma
- **Exocrine glands (M3):** : ↑ salivary, lacrimal, sweat, bronchial, gastric HCl secretions.
- **CNS (M1):** ↑ vomiting, memory, muscle tone

❑ On Nicotinic receptors:

- (Nn) → Stimulation of ganglia and adrenal medulla to release Ep. & NE. → tachycardia and a rise in BP.
- (Nm) → initially produces twitching, High concentration prolonged depolarization → paralysis

Parasympathomimetic

1. Directly acting: Cholinergic agonists

a) Choline esters

- **Preparation:** Methacholine, carbachol and bethanechol. (Synthetic Choline Esters)
  - 4ry amine drugs → low lipid solubility & poor CNS action.
  - Not hydrolyzed by ChE → Longer duration of action:
- The advantages over acetylcholine:
  - given orally due to better absorption. More selective actions.

1. Methacholine:

- Acts mainly on muscarinic receptors.
- Hydrolysis by true cholinesterase only.
- More selective action on C.V.S.
- Used mainly in peripheral vascular diseases and paroxysmal atrial tachycardic

2. Carbachol:

- It stimulates both muscarinic and nicotinic receptors
- No hydrolysis by AChE enzyme.
- More selective action on Eye.
- It is used as local eye drops to ↓ IOP in glaucoma.

3. Bethanechol:

- Acts mainly on muscarinic receptors.
- No hydrolysis by AChE enzyme,
- More selective action on GIT& urinary tract.
- It is used as
  - Post-operative non-obstructive paralytic ileus.
  - Post-operative non-obstructive urine retention (orally or S.C.).

b) Natural plant parasympathomimetic (Cholinomimetic alkaloids)

1. Pilocarpine

- 3ry amine alkaloid form plant origin. → Lipid soluble → pass BBB → CNS action.
- No hydrolysis by AChE enzyme, .
- Acts mainly on muscarinic receptors: selective M3 agonist on:

a. Eye: miotic used for:
- Treatment of glaucoma (drug of choice for emergency lowering of I.O.P).
- Counter acting mydriatics after fundus examination,

b. Exocrine glands: ↑ secretion—• used by orally in treatment of dry eye and dry mouth (xerostomia) associated with Sjogren's syndrome

2. Cevimeline:

- It is synthetic drug.
- Acts mainly on muscarinic receptors: Selective M3 agonist in exocrine secretions.
- Used mainly orally in treatment of dry eye and dry mouth (xerostomia) associated with Sjogren's syndrome

❖ Side effects of cholinergic drugs:

- nausea, vomiting, salivation, bronchospasm, hypotension, bradycardia and diarrhea.
- carbachol cause muscle twitches due to nicotinic receptor Nm stimulation;
- Can be blocked by atropine (antimuscarinic drug, 0.5-1 mg parentally)

❖ Contraindications:

1. Bronchial asthma
2. Peptic ulcer.
3. Ischemic heart diseases (angina pectoris) as hypotension decreases coronary blood flow.
4. Hypotension & bradycardia.
5. Thyrotoxicosis (increased atrial conduction atrial fibrillation.
6. IV and IM injection → severe bradycardia and hypotension (treated by atropine).

Parasympathomimetic

2. Indirectly acting: Anticholinesterases (ChE inhibitors)

- Bind with acetylcholinesterase enzyme → enzyme inactivation → ↑ ACh in synaptic space → ↑ cholinergic action.
- Act on both muscarinic and nicotinic receptors.

a) Reversible anticholinesterases:

1. Edrophonium (Short acting: 2-10min-reversible):

- 4ry amine drugs → not pass BBB. (no CNS effects).
- More selective action on skeletal muscles.
- **Used mainly** IV in:
  - Diagnosis of myasthenia gravis.
  - Differentiation between of myasthenia and cholinergic crisis
  - In curare poisoning, edrophonium is preferred because of its rapid onset of action.

2. Physostigmine (Intermediate acting 2-4 hours-reversible):

- 3ry amine from plant → lipid soluble → pass BBB.
- Selective action on eye, GIT and bladder and C.N.S. Stimulation.
  - **Muscarinic effects**: hypotension, bradycardia, salivation, lacrimation, diarrhea, miosis.
  - **Nicotinic effects:** skeletal muscle contraction.

- **CNS effects:** headache, improves memory and convulsions.

- **It is used in:**
  - Atropine poisoning (central & peripheral atropine antagonist).
  - Alzheimer's disease,.
  - as Eye drops for Glaucoma

- **Side effect:**
  - Bradycardia-hypotension -bronchospasm and ↑ bronchial secretor- ↑ HCI secretion -CNS stimulation (convulsions).

3. Neostigmine:

- 4ry amine drugs → not pass BBB. (no CNS effects)
- It is similar to physostigmine in mechanism and effects but it has no CNS actions.
- Selective action on GIT, bladder and voluntary skeletal muscles.
- stimulates the N_M receptors at NMJ. → improves muscle in patients with myasthenia gravis.
- **It is used in**:
  - myasthenia gravis (with atropine).
  - Antidote Curare poisoning e.g. D-tubocurarine.
  - Non-obstructive post -operative urine retention and paralytic ileus.

- **Side effect:** As physostigmine but no CNS manifestations

4. Pyridostigmine :

- 4ry amine compounds.
- Longer duration of action than neostigmine. (3-6 hours)
- Preferred in myasthenia'(↑ duration, fewer side effects ; ↑ selectivity on skeletal muscles compared to neostigmine)

5. Tacrine, donepezil, and rivastigmine:

- Selective action on CNS.
- Used in Alzheimer disease to delay the progression of disease.
- Tacrine is hepatotoxic.
- Donepezil, & Rivastigmine are safer than tacrine
- GIT disturbances are the main side effects.

b) Irreversible Anticholinesterases (Organophosphorus Compounds)

- Irreversible binding to acetylcholinesterase enzyme →↑ of endogenous A.Ch. → ↑MR & NR
- Highly toxic and some of them are used as
  - **Insecticides**: as organophosphates: parathion and malathion)
  - **War gases**: (also known as nerve gases & tear gases): Sarin.
  - Isoflurophate and echothiophate: High long duration of action. (may be for one week), Used in chronic treatment of open angle glaucoma as eye drops or ointment.

Parasympathomimetic

- 3ry amine compounds→. easily pass B.B.B. and cell membrane, except echothiophate.
- They are easily absorbed through GIT, mucous membrane and skin, except echothiophate.

❑ Organophosphorus toxicity:

- Bradycardia and hypotension.
- Bronchospasm.
- Miosis.
- ↑ Salivation and sweating.
- Convulsion and coma.
- May lead to depression of respiratory and cardiovascular centers → death due to respiratory failure.

❑ Treatment of toxicity by acetylcholinesterase inhibitors:

- Pralidoxime (PAM): as cholinesterase reactivator (removing the organophosphate compounds from enzyme but effective if given early).
- Atropine (antagonize muscarinic effects centrally and peripherally).
- Anticonvulsants as diazepam.
- Artificial respiration or aminophylline (bronchodilator).

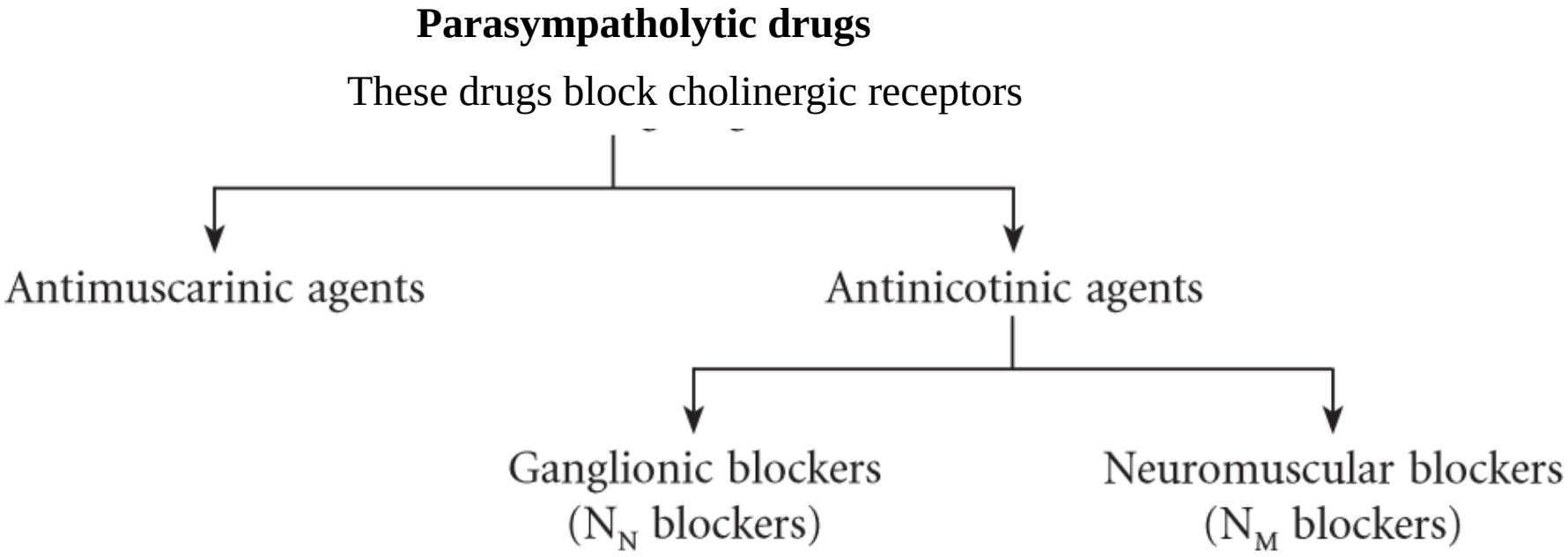
Autonomic Nervous System (A.N.S.)

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Parasympatholytic drugs

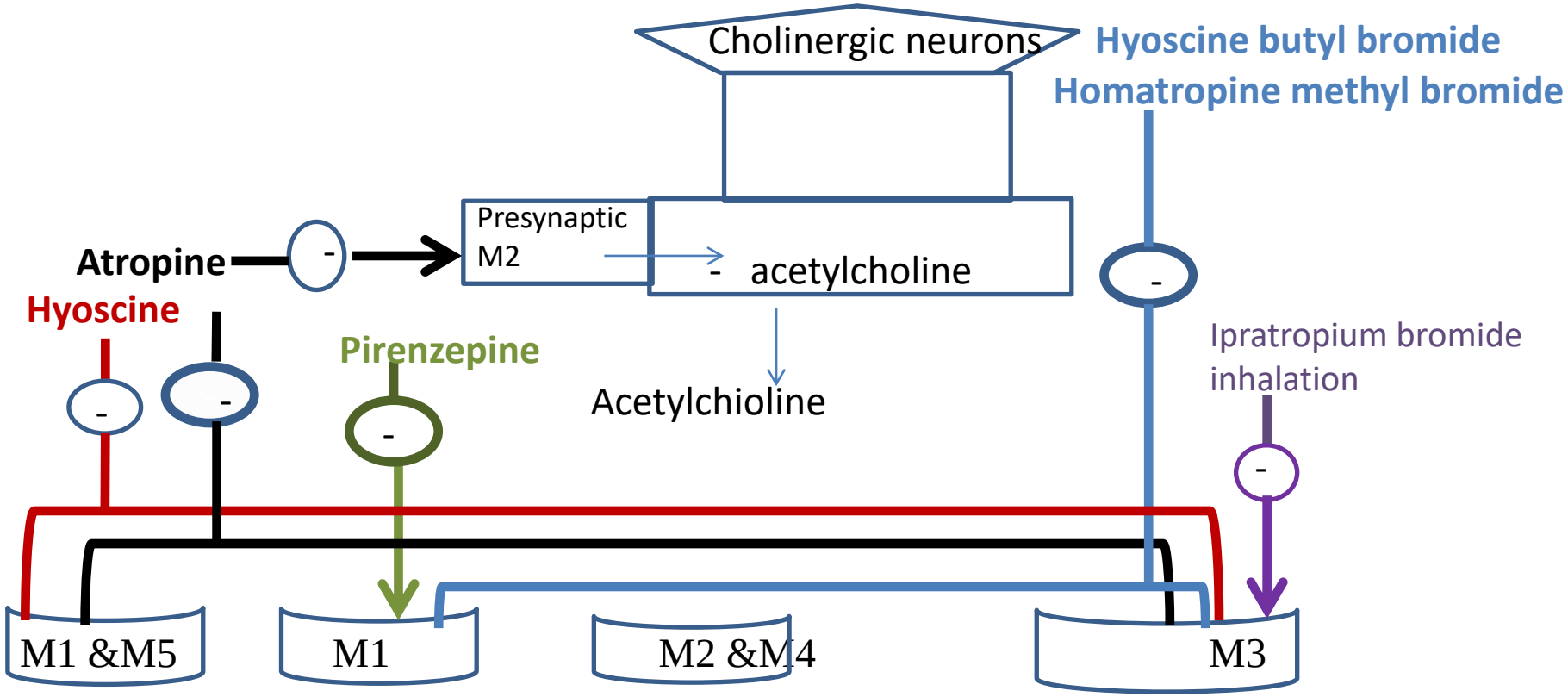
Parasympatholytic drugs



❖ Antimuscarinic agents:

- They block the action of muscarinic receptors by competition with acetyl choline at receptor site.
- Also known as: antimuscarinic drugs, muscarinic blockers, and anticholinergic drugs

Mechanism of action of Antimuscarinic drugs



CNS stimulation -

-Increase gastric HCl -

-Decrease heart rate
-Increase atrial conduction
- No effect on ventricles

-Smooth muscle contraction (UT& GIT & uterus & bronchi
-Increase all secretions except milk
-Miosis , increase aqueous drainage

Parasympatholytic drugs

- **Antimuscarinic drugs**

Quaternary ammonium antimuscarinic drugs	Tertiary ammonium antimuscarinic
They contain +ve charged nitrogen atom	They contain non-charged nitrogen atom
poorly absorbed GIT & mucous membrane → not pass BBB (not effect in CNS)	Easily absorbed GIT& mucous membrane → pass BBB (in CNS)
They block muscarinic receptors in low doses and nicotinic receptors at high doses → skeletal muscle relaxant	They block muscarinic receptors at low dose and no effect on nicotinic receptors, not affect skeletal muscle
They block nicotinic receptors in autonomic ganglia in large doses	They have no effect on autonomic ganglia
More effective on GIT& urinary tract due to both muscarinic and ganglionic blockade	Less effective on GIT& urinary tract because they block muscarinic receptors with no effect on autonomic ganglia
Preparations -Hyoscine butyl bromide -Homatropine methyl bromide - Glycopyrrolate	**Preparations** -Hyoscine. -Atropine -Homatropine Cyclopentolate -Tropicamide

Parasympatholytic drugs

▪ Antimuscarinic drugs

a) Atropine & Atropine Substitutes

1. Atropine

- 3ry amine, natural antimuscarinic agent from alkaloid of belladonna → well absorbed from GIT if given orally or from conjunctiva after ocular instillation & can cross BBB.
- Partially metabolized by the liver (about 40%) and partially excreted in urine unchanged (about 60%). Acidification of urine →↑Its urinary excretion.

❖ Mechanism of action:

- Reversible competitive muscarinic blocker (non-selective competitive antagonist, M1, M2 and M3).
- It blocks presynaptic followed by post synaptic muscarinic receptors.

❖ Pharmacological actions:

- **CNS:**
  - ➢ Initial CNS stimulation (blocks M2 receptors) → initial brady cardia, Respiratory stimulation,
  - ➢ Late CNS depression → Amnesia, Sedation, Antiemetic (M1 blocker), ↓ muscle tone (Antiparkinsonian).
  - ➢ Toxic doses (large) → convulsions, paralysis followed by coma and death due to depression of R.C.

Parasympatholytic drugs

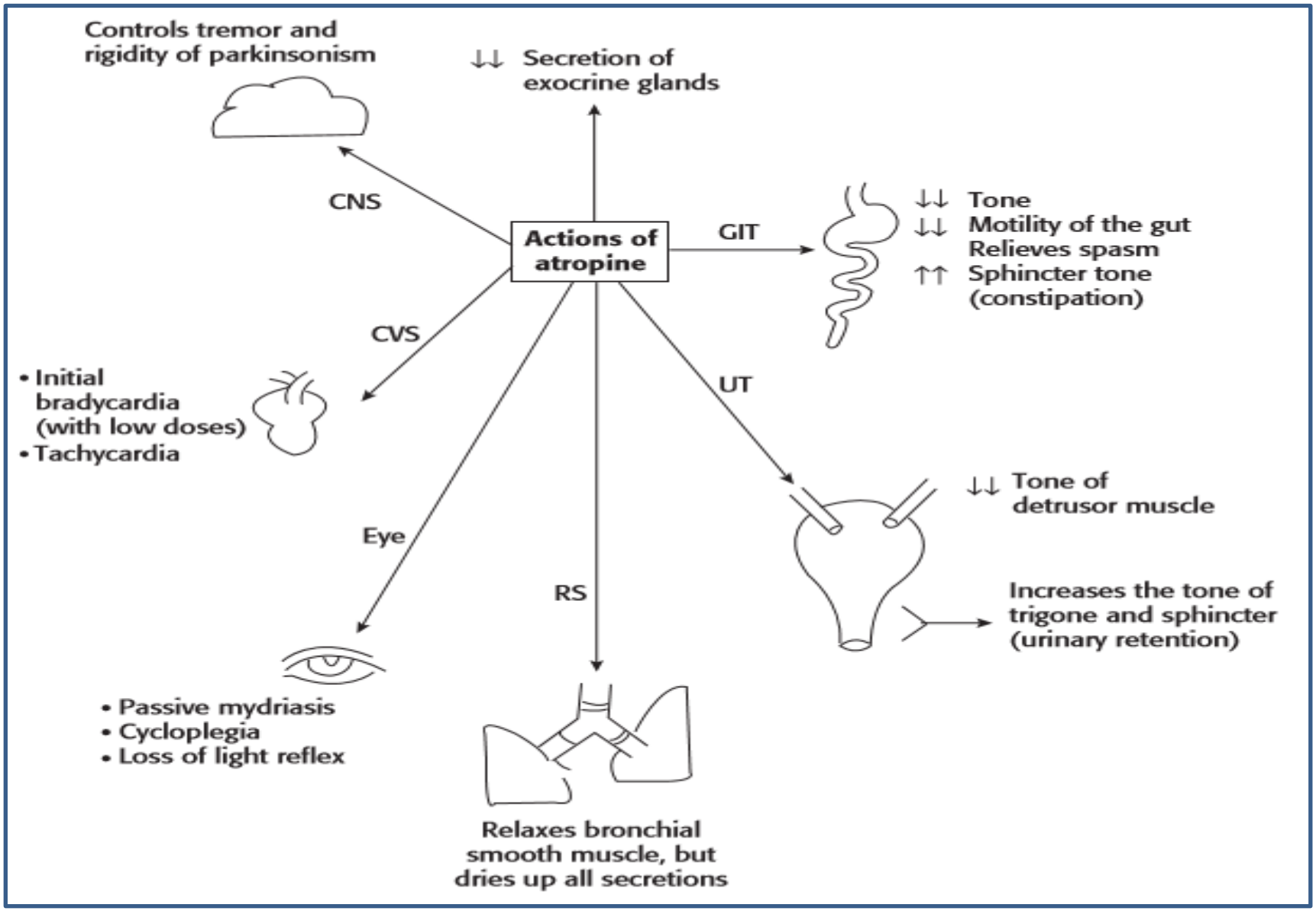
- **Eye:**
  - Paralysis of circular pupil muscle → Passive mydriasis.
  - Paralysis of ciliary muscle → cycloplegia and loss of accommodation for near vision.
  - ↑ IOP → closed angle glaucoma.
  - ↓ Lacrimation. (dryness)

- **CVS**: Initial bradycardia (presynaptic M2 inhibition) followed by tachycardia (postsynaptic M2 inhibition) & ↑ AVN conduction and Vasodilation (due to histamine release).

- **GIT:** relaxes wall & contracts sphincters → constipating & antispasmodic
- **Urinary bladder**: contraction of urinary bladder sphincter → urine retention.
- **Bronchodilatation.**

- ↓ **Secretions** (saliva, sweat, Lacrimal and bronchial secretions) → ↓ all secretions (except milk, urine, and bile) → drying effect. And ↓ gastric HCl secretion

Parasympatholytic drugs



Actions of atropine. UT, urinary tract.

❑ Clinical Uses of Atropine & atropine Substitutes

❖ Therapeutic uses of Atropine:

- **Pre-anesthetic medication** → ↓ secretions - dilates bronchi - antiemetic- inhibits reflex bradycardia – stimulates respiration.
- Bradycardia & Heart block due to B-Blockers drugs, Digitalis & Myocardial infarction.
- Organophosphate poisoning- Parasympathomimetic poisoning .
- Cycloplegic in children (atropine is preferred to atropine substitutes because of its greater efficacy)
- Travelers' diarrhea ((plus diphenoxylate).

❖ Therapeutic uses of Atropine Substitutes: (more selective → fewer side effects)

I. Hyoscine (Scopolamine, 3ry amine, natural antimuscarinic)

- Stronger anti muscarinic action on the CNS, eye and exocrine.
- More effect on CNS → sedation, drowsiness, amnesia, anti parkinsonian and potent antiemetic.
- **Used mainly as:**

- Preanesthetic medication in thyrotoxic & Cardiac patients (pure antagonist; no initial bradycardia).
- Vomiting of motion sickness & Meniere's disease (preferred as it is more effective than atropine). → can be administered orally or as a transdermal patch

Parasympatholytic drugs

II. Synthetic atropine substitutes

1. Mydriatic cycloplegics (Homatropine-Tropicamide-Cyclopentolate)

- 3ry amine, Semisynthetic atropine derivative.
- Shorter duration of action: 1 day (Homatropine-Tropicamide), 6 h (Cyclopentolate)
- Antagonized completely by miotics (physostigmine and pilocarpine).
- Used for fundus eye examination, Cycloplegias for measurement of refractive errors. preferred to atropine (except in children).

2. Antisecretory - Antispasmodics

❑ 4ry amine drugs → less absorption- less CNS side effects, In large doses, they inhibit nicotinic receptors in autonomic ganglia and skeletal muscles, more potent than atropine in inhibiting GIT.

1. Glycopyrrolate → anti-secretory , Used for preanaesthetic medication, Sialorrhea (hypersalivation)

2. Hyoscine butyl bromide → antispasmodic in renal, biliary & intestinal colic & in irritable bowel syndrome. Used IV, IM, orally & rectally.

3. Pirenzepine & telenzepine → anti-secretory, Selective M1 blockers (↓ HCl secretion) → Used in peptic ulcer.

Parasympatholytic drugs

3. Urinary atropine substitutes

- Oxybutynin, & tolterodine.

- More selective action on M3 receptors in urinary bladder.
- Used in urinary incontinence and nocturnal enuresis.

4. Antiparkinsonian atropine Substitutes:

- Benztropine- Benzhexol.

- 3ry amines and can easily pass BBB.
- Used in Parkinsonism → ↓ rigidity and tremors.
- Drug induced Parkinsonism: preferred to dopaminergic drugs.

5. Bronchial Asthma atropine Substitutes :

As: ipratropium- Tiotropium

- 4ry compounds. They are given by inhalation.
- Produce bronchodilatation with no effect mucous secretion or ciliary function.
- Tiotropium (24 h) is longer acting than ipratropium (6 h).
- Used in prophylaxis of bronchial asthma, chronic obstructive pulmonary diseases (COPD).

Parasympatholytic drugs

❖ Adverse effects:

- Tachycardia, palpitation, and anginal pains in anginal patients
- Dry mouth (Xerostomia), Blurring of vision, loss of accommodation to near vision (due to cycloplegia), dryness of the eye (xerophthalmia).
- ↑ lOP which may precipitate acute glaucoma especially in old patients.
- fever (red hot dry skin)
- Constipation & Urinary retention especially in patients with senile enlarged prostate.
- drowsiness, hallucination, and delirium if used in large doses.

❑ **NB**: Antispasmodics drugs (4ry amine) in Large doses → cause hypotension and sexual dysfunction (impotence) due to inhibition of nicotinic receptors, blockade of ganglia.

❖ Contraindications:

- Glaucoma, . benign prostatic hypertrophy.
- Tachyarrhythmias., angina pectoris. Constipation

❖ Treatment of atropine poison :

- Gastric lavage.
- Cooling blankets: to treat hyperthermia
- The antidote for severe atropine poisoning is physostigmine (antagonizes central & peripheral effects).
- Diazepam: to control CNS excitement

Parasympatholytic drugs

❖ Ganglion Blockers

- Block Nn receptors in autonomic ganglia → ↓ sympathetic and parasympathetic system.
- No selective ganglion blockers, so they are rarely used therapeutically.

❑ The ganglionic blockers have:

- **Blockade of parasympathetic ganglia** → atropine-like' action on heart (palpitation and tachycardia), eye (mydriasis and cycloplegia), GIT (dryness of mouth and constipation), bladder (urinary retention), impotence in males and decreased sweat secretion.
- **Blockade of sympathetic ganglia** → marked postural hypotension.

❑ Competitive ganglion blockers:

1. Trimethaphan: Not pass BBB, Short-acting ganglion blocker. Given by I.V. infusion in emergency hypertension.

2. Mecamylamine: Pass BBB, Longer action than Trimethaphan, Given orally in moderate to severe hypertension.

❖ Mechanism of action as antihypertensives:

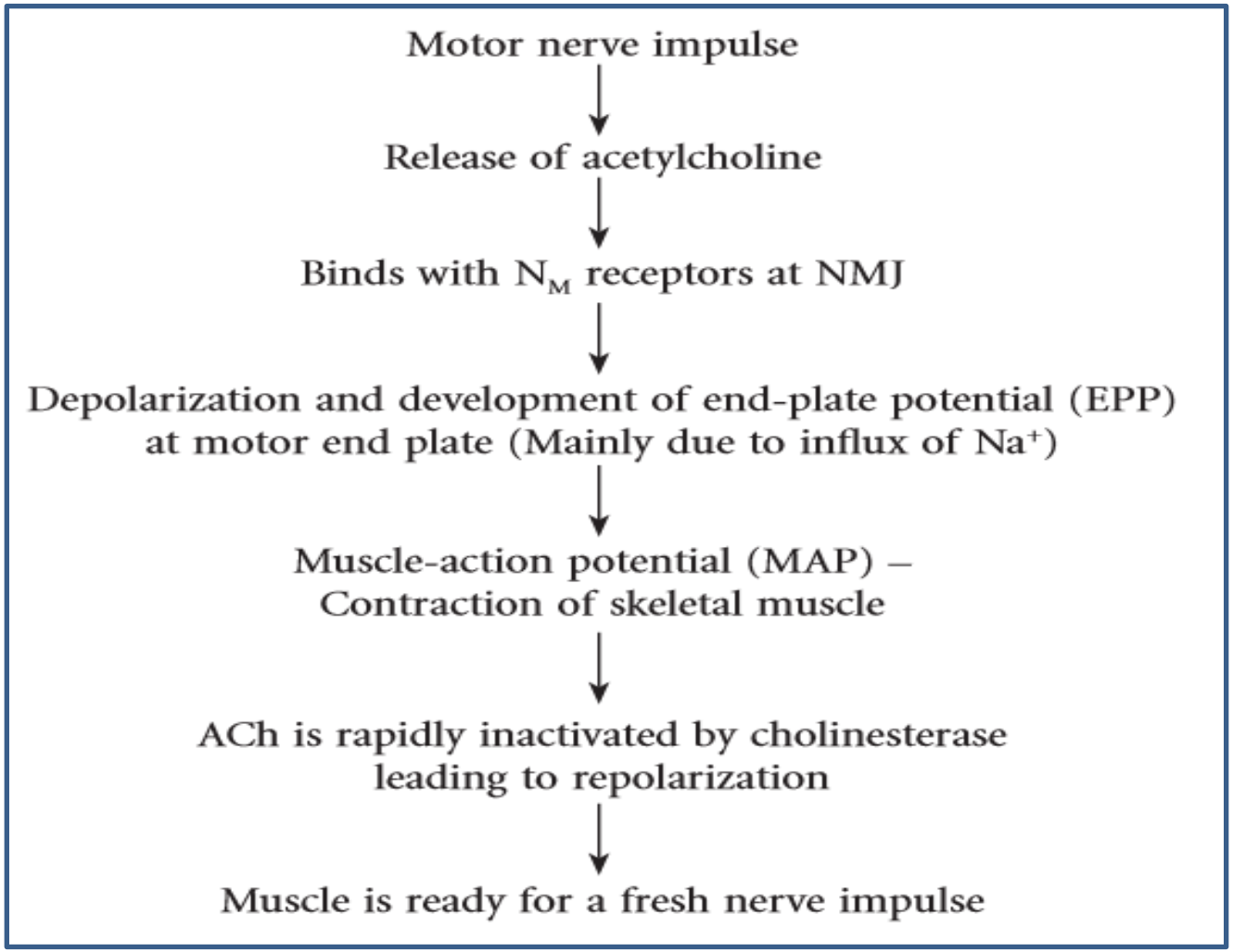
- They block competitively Nn-receptors in adrenal medulla and in sympathetic ganglia → ↓ adrenaline and noradrenaline from adrenal medulla → V.D. → ↓ T.P.R. and A.B.P.

❖ **Adverse effects:** "Atropine-like + Postural hypotension + Sexual dysfunction in males".

Parasympatholytic drugs

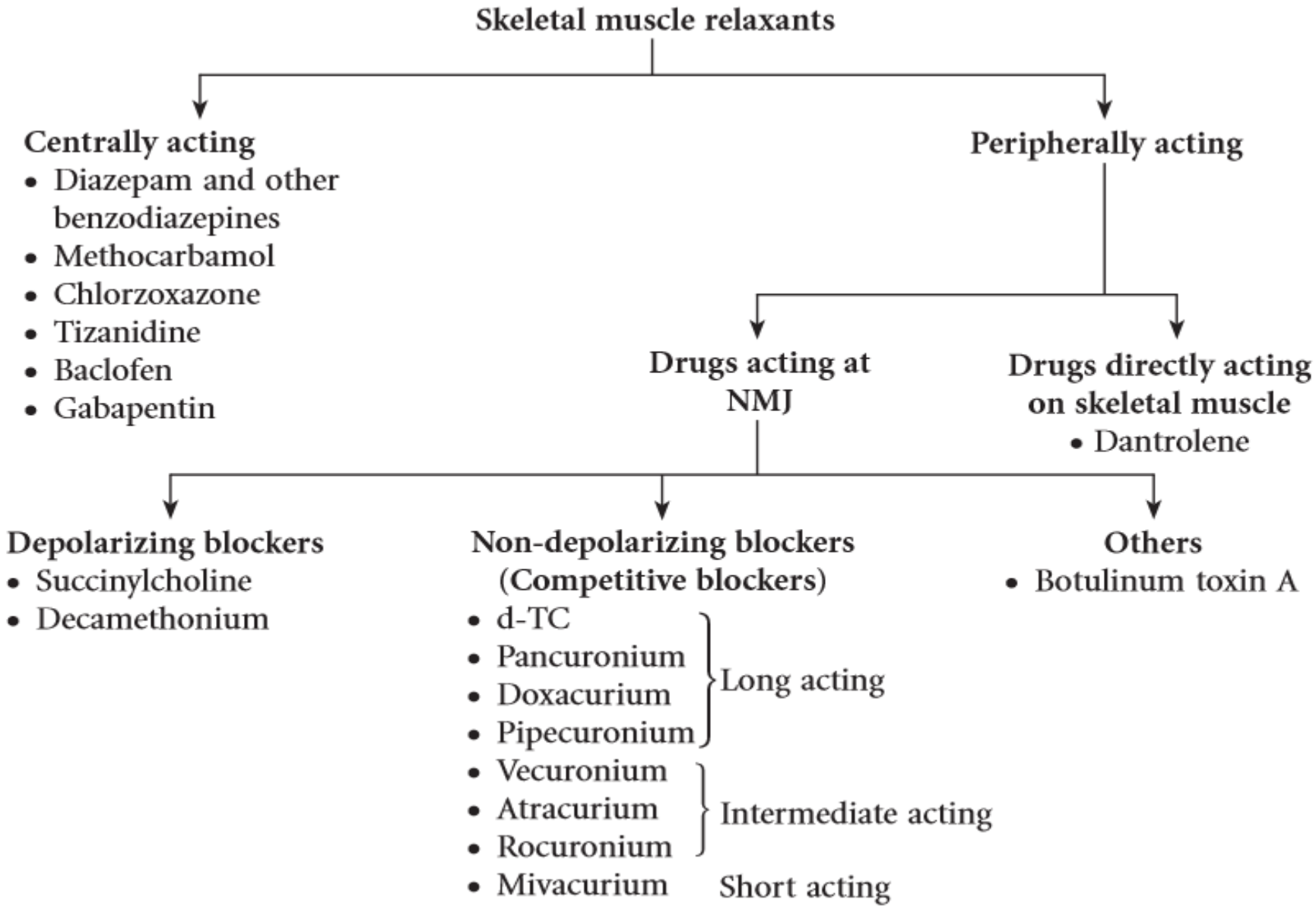
❖ Neuromuscular blockers

- Block nicotinic receptors on skeletal muscles at neuromuscular junction → muscle relaxation.


Motor nerve impulse
Release of acetylcholine
Binds with N_M receptors at NMJ
Depolarization and development of end-plate potential (EPP) at motor end plate (Mainly due to influx of Na^+)
Muscle-action potential (MAP) – Contraction of skeletal muscle
ACh is rapidly inactivated by cholinesterase leading to repolarization
Muscle is ready for a fresh nerve impulse

Physiology of skeletal muscle contraction

Parasympatholytic drugs



Parasympatholytic drugs

❖ Neuromuscular blockers

- Classified to Non-depolarizing and depolarizing neuromuscular blockers.

	Competitive (Non-depolarizing)	Non competitive (depolarizing)
Mechanism of action	They block Nm receptors at neuromuscular junction by competition with acetylcholine at NM receptors.	They bind to Nm receptor → initial depolarization (Stimulation &Twitches) followed by maintained depolarization (Block & Paralysis).
Action	Muscle relaxation in: face and neck→ Limb & Trunk → intercostal→ Lastly the Diaphragm.	Initial contraction followed by progressive relaxation of skeletal muscles: arm →neck & face →Diaphragm→ then intercostal
Nn receptors	Noncompetitive Inhibition (by binding to Na^+ channels) → ganglion blockade (hypotension, tachycardia)	Stimulation → hypertension and increase GIT motility
Histamine release	Most of them increase histamine release → (bronchospasm, hypotension)	No
Preparations	**Short acting**: less than 10 minutes: mivacurium due to inactivation by psudocholineesterase **Intermediate acting** (10-20 minutes): due to extensive hepatic metabolism (atracurium , vencuronium ,cisatraccuonium rocuronium). They have mild histamine release	Succinylcholine: It is short acting because it is metabolized by plasma pseudocholine esterase

	Competitive	Non competitive
Preparations	**Long acting**: no hepatic metabolism excreted unchanged in urine. They are divided into **1-Potent histamine releasers, mild ganglion blockers:** D-tubocurarine, mecholine. **2-Potent ganglion blockers**, mild histamine releasers (tachycardia): Fasidenium, gallamine , alcuronium **3-Norepinepinephrine releasers** (hypertension) Pancuronium, pipracuronium, doxacurium	
Therapeutic uses	-Long & intermediate acting preparations (10-20 minutes): Adjuvant during general anesthesia -Treatment of convulsive states e.g. tetanus. -Induction artificial respiration to block normal respiratory movements Mivacurium used as succenylcholine	-Facilitate Endoscopy e.g . Endotracheal intubation -Electroconvulsive therapy to reduce muscle injury. -Diagnosis of Myasthenia gravis
Side effects	-Hypotension due to histamine release and ganglion blockade, -Bronchospasm due to histamine release -Hypertension due to increase norepinephrine release (Pancuronium, pepercuonium, doxacuronium) -Overdose causes prolonged respiratory depression (treated by atropine followed by neostigmine)	Hypertension due to sympathetic ganglion stimulation, -**Succinylcholine apnea**: prolonged respiratory depression due to congenital deficiency of psudocholine esteras (Treated by: artificial respiration, fresh plasma transfusion (provide pseudocholineesterase), neostigmine) - Vomiting due to contraction of abdominal muscles

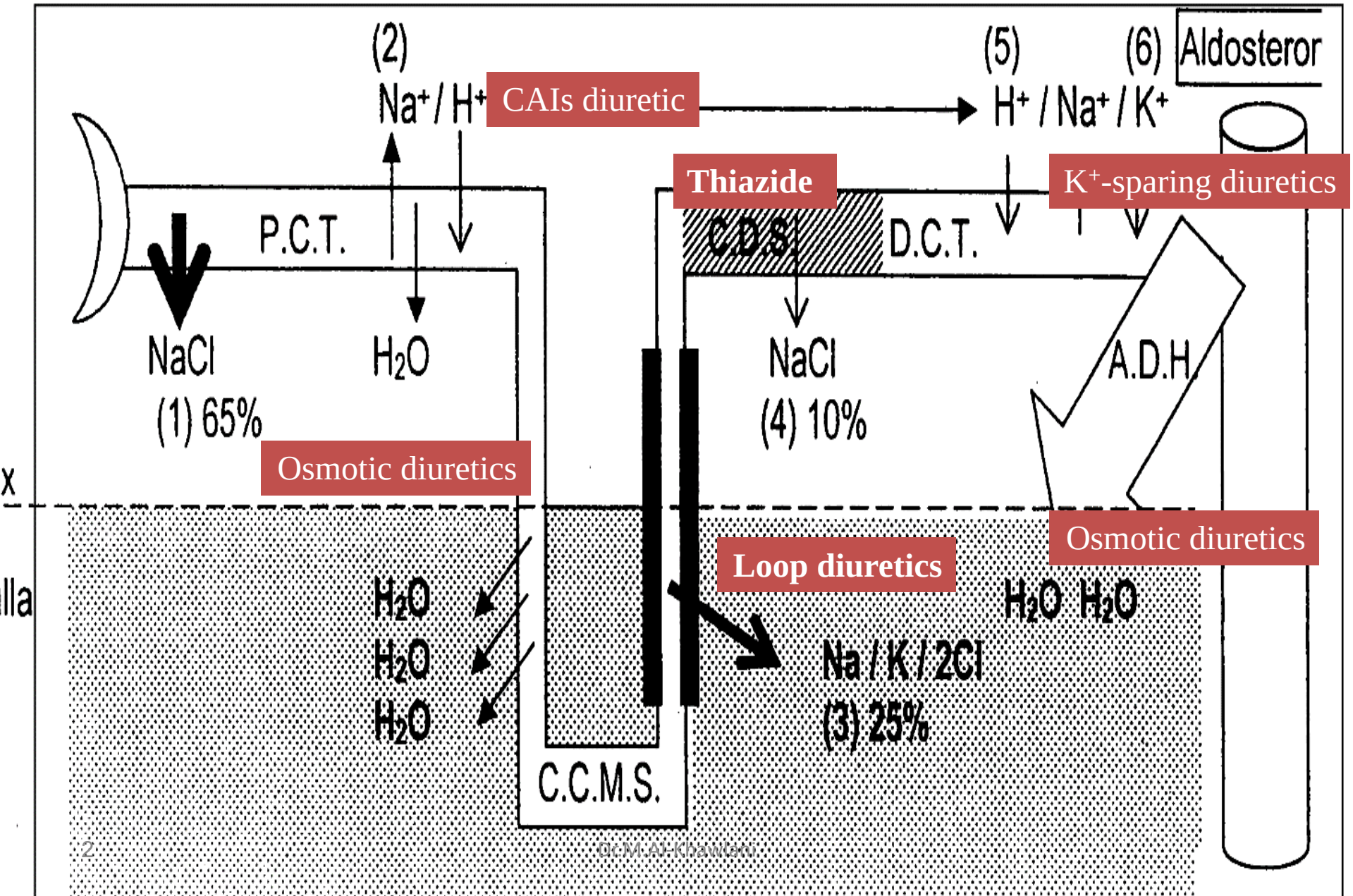
	Competitive	Non competitive
Side effects	-Atracuronium undergo partial non-enzymatic spontaneous metabolized to toxic tertiary amine metabolite laudanosine which causes CNS stimulation & epilepsy by blocking GABA receptors and hypotension by α_1 blocking action	-Increase intraocular pressure due to contraction of lid and extraocular muscles -Muscle injury and hyperkalemia, - Malignant hyperthermia due to initial muscle contraction (treated by dantrolene).
Reversed by	Neostigmine (antidote), Tetanic contraction, potassium	General and local anesthetics, antibiotics (tetracycline, aminoglycosides and polymexin
Augmented	- General and local anesthetics, antibiotics (tetracycline, aminoglycosides and polymexin) - quinidine &procainamide - Renal or hepatic impairment	- Neostigmine, Tetanic contraction, K^+ - Decrease in pseudochoineesterase either congenital, hepatic impairment or nutritional deficiency

Diuretics agents

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Assist. Professor of pharmacology and Toxicology

Physiology of the Kidney



Segment	Function	Diuretic with major action
1) Proximal Convoluted Tubules (PCT)	▪ **Site 1:** Active reabsorption of Na+ (65%). ▪ **Site 2:** Some Na+ is reabsorbed in exchange for H+ under the effect of Carbonic Anhydrase Enzyme (C.A.E.) ▪ Reabsorption of all filtered K+, glucose, amino acids, and drugs. ▪ Organic acids & bases are Reabsorbed & Secreted in P.C.T. e.g. Uric acid, penicillin, Diuretics &Probenecid.	▪ **Carbonic anhydrase inhibitors**
2) Descending Loop Of Henle (LOH)	▪ Passive reabsorption of water due to hypertonicity of the medullary interstitium.	Non
3) Thick ascending limb of loop of Henle (TAL)	▪ **Site 3:** Active reabsorption of 25% of filtered Na+/K+/Cl ▪ Secondary reabsorption of Ca2+ and Mg2+	▪ **Loop diuretics**

Segment	Function	Diuretic with major action
5) Distal Convoluted Tubules (D.C.T & Collecting Tubules:	▪ **Site 4:** Active reabsorption of 10% of filtered Na+ and Cl (Early part of D.C.T. =Cortical Diluting Segment) ▪ **Site 5:** Na• /H+ Exchange under the effect of C.A.E. ▪ Ca2+ reabsorption under PTH ▪ **Site 6:** Na+ /K+ (2–5%) Exchange under the effect of Aldosterone ▪ Collecting tubules (CT): Reabsorption of water under the influence of ADH.	▪ **Thiazides** ▪ **Carbonic anhydrase inhibitors** ▪ **K+-sparing diuretics**

NB: Thiazides, loop diuretics and carbonic anhydrase inhibitors are organic acids → Secreted by organic acid secretory systems → compete with Secretion of other organic acids such as uric acid → hyperuricemia

Diuretics

- Diuretics are drugs that increase Na and water excretion in urine

❖ Classification of diuretics:

Renal diuretic: they ↓ Na+ reabsorption from the nephron on the kidney and classified into:

- **Thiazide diuretics:** they are moderate efficacy
- **Loop diuretics:** they are high efficacy diuretics .
- **K^+-sparing diuretics:** they are low efficacy diuretics- they are either aldosterone antagonists as spironolactone, or non-aldosterone antagonists as amiloride
- **Carbonic anhydrase inhibitor (CAIs):** They are low efficacy and are self-limiting because they cause acidosis.
- **Osmotic diuretics:** ↑ the osmotic pressure of tubular fluid → ↓ water reabsorption by renal tubules e.g. mannitol

.**NB:** Thiazide, loop diuretics, K+ -sparing diuretics, and CAIs are known as "Natriuretics because they increase urinary excretion of Na+ with its iso-osmotic water.

Diuretics

1. **Thiazide Diuretics:** medium-efficacy. (maximum excretion of Na+ is only 10%)

❖ Preparations:

1. Thiazides group: Hydrochlorothiazide, Short acting (2-4 times/d). structurally related to sulfonamides

2. Thiazide-like diuretics: (long acting > 24h)

- **Chlorthalidone**
- **Metolazone** (effective in impaired renal function)
- **Indapamide**: used mainly in hypertension, less metabolic side effects.

❖ Pharmacokinetics:

- Well absorbed orally, metabolized in the liver.
- Slow onset of action (produce diuresis within 1–2 hours), but they have a longer duration of action than loop diuretics
- Excreted in PCT by active secretion → compete with the secretion of uric acid → hyperuricemia.

Thiazide Diuretics

❖ Mechanism of action:

- Inhibit NaCl reabsorption in the early part of DCT →↑ Na+ excretion →↑ exchange of --
  - Na+/H+ → metabolic alkalosis
  - Na+/K+ → K loss (hypokalemia) →Cardiac arrhythmia, Muscle pain, ↓ insulin secretion. Hyperlipidemia.

- ↑ Ca2+ reabsorption by Na+/Ca2+ exchange → Hypercalcemia

- Loss of Na+, K+, Cl-, H+, Mg2+ in urine

- Arterial Vasodilator action due to open of k channels → Antihypertensive effect.

NB:

- ❑ The action of thiazides depends on renal PG production→ their actions can be inhibited by NSAIDs under certain conditions
- ❑ Not effective in cases of renal impairment → metolazone is effective in impaired renal function.

Thiazide Diuretics

❖ Therapeutic uses:

1) **Mild and moderate edema:** Cardiac, Renal, or Hepatic edema

2) **Mild and moderate hypertension:** Direct V.D. & ↓ Blood volume
   - Drug of choice in old patients, low rennin hypertension
   - Thiazides are preferred to loop diuretics in treatment of hypertension (**except** in cases of emergency hypertension and renal impairment)

3) **Heart failure:** mild-to-moderate cases

4) **Hypercalciuria:** treat nephrolithiasis (Ca stones), because they inhibit urinary Ca2+ excretion.

5) **Nephrogenic diabetes insipidus**

❖ Adverse effects

1) Hypokalemia (causes fatigue, and cardiac arrhythmias).
2) Metabolic alkalosis and hypotension.
3) Hyperuricemia → may precipitate acute gouty attacks.
4) Hyperglycemia: due to both ↓ pancreatic release of insulin and ↓ tissue utilization of glucose.

Thiazide Diuretics

5) Hyperlipidemia: due to ↑ cholesterol and LDL.
6) Hypomagnesemia (may also precipitate digitalis toxicity).
7) Allergic reactions: thiazides are derivatives of sulfonamides; skin rash, and dermatitis

❖ Contraindications :

1) Diabetes mellitus (Hyperglycemia).
2) Renal insufficiency
3) Gout (Hyperuricemia).
4) Allergy to thiazides and Sulfonamides groups

❖ Drug-drug interaction

- Digitalis
- NSAIDs

Loop diuretics

2. Loop diuretics (high ceiling diuretics)

❖ Preparations:

1. **Sulfonamide derivatives**:
   - Frusemide (Lasix)®, : oral dose 80mg (40-120); IV dose 40mg (20-60mg).
   - Bumetanide: (40 times more potent): oral and IV dose 1-5 mg.
   - Torsemide: oral (10-100mg)

2. **Non-sulfonamide derivatives**: **Ethacrynic acid**

❖ Pharmacokinetics:

- They are absorbed from the GIT and secreted into the lumen of the PCT by an organic acid excretory system.
- The absorption of furosemide is erratic but bumetanide is complete
- Furosemide has a **rapid onset of action** (2–5 min of IV, 10–20 min after IM and 30–40 min after oral) (useful in emergencies), and **short duration of action** (2–4 h), whereas, Torsemide lasts (4–6 h)
- Highly bound to plasma proteins → displace other drugs as warfarin

Loop diuretics

❖ Mechanism of action:

- Inhibit Na+/ K+ / 2Cl-co-transporter in TAL of Henle's loop →↓ reabsorption of Na+, K+, & Cl →↑ Na+ excretion →↑ exchange of:
  - Na+/H+ → metabolic alkalosis
  - Na+/K+ → K loss (hypokalemia)

- ↑ Ca2+ & Mg2 excretion

- Loss of Na+, K+, Cl-, H+, Ca2+, Mg2+ in urine

- They ↑ renal PGE2 and PGI2 production → VD and ↑RBF and GFR.→ useful in acute renal failure
  - NSAIDs inhibit PG synthesis and antagonize this effect of loop diuretics.

- Venodilator action → adds to their benefits in acute pulmonary oedema.

Loop diuretics

❖ Therapeutic uses:

1) **Emergency case:** (as it is rapid with potent diuretic agent ;can be given IV)
   - in Acute Pulmonary edema and cerebral edema (Venodilation).
   - Hypertension: loop diuretics are preferred to thiazides in the following conditions:

- ❑ Hypertension in patients with renal failure & heart failure**.**
- ❑ Emergency hypertension.
- ❑ Sever & resistant hypertension

2) **Treatment of refractory and severe edema**
   - Refractory edema of severe CHF & renal insufficiency.
   - Refractory edema of liver cirrhosis (added of spironolactone).
   - Acute renal failure (↑ renal blood flow).

3) **Electrolyte & Acid- base Disturbances**
   - Acute hypercalcemia (IV furosemide)
   - Hyperkalemia because it increase potassium loss in urine

Loop diuretics

❖ Adverse effects:

1) Hypokalemia (causes fatigue, and cardiac arrhythmias), hypotension.
2) Hypocalcemia, Hyperuricemia, Hyperglycemia, Hyperlipidemia (↑ cholesterol and LDL), Hypomagnesemia and metabolic alkalosis
3) Hypersensitivity (and cross allergy with sulfonamides with some loop diuretics).
4) Ototoxicity: damage of the 8th cranial nerve → may cause deafness, (especially with aminoglycosides).

❖ Contraindications

1) Allergy to loop diuretics and sulfonamides.
2) Diabetes mellitus (Hyperglycemia).
3) Gout (Hyperuricemia).
4) With other ototoxic drugs as aminoglycosides

❖ Drug interactions:

1. **With Digitalis**: Hypokalemia and hypomagnesemia induce digitalis toxicity.
2. **With NSAIDs**: NSAIDs antagonize partially the diuretic action of loop diuretics because they reduce vasodilator PGs which increase RBF, and → Na+ and H2O retention→↓ antihypertensive effect of loop or thiazide diuretics
3. **With warfarin**: Frusemide displaces Warfarin from plasma protein binding sites.
4. Aminoglycosides antibiotics: ototoxic.

Potassium Sparing Diuretics

3. Potassium Sparing Diuretics (Weak diuretics; excrete only 5% of Na+ filtrate)

- Inhibit Na^+/K^+ and Na^+/H^+ exchange at the DCT → ↑ excretion of Na^+/ cl and water (Low Efficacy) →↑ retention of K^+ (hyperkalemia) and H^+ (metabolic acidosis).

- Inhibit Na+/K+/H+ exchange by two different mechanisms:

1- **Aldosterone antagonists**: (delayed onset of action, requires 3-4 days).
e.g. **Spironolactone** - **Eplerenone.** They are competitive antagonists with aldosterone for specific aldosterone receptors in cells of DCT

2- **Non-Aldosterone antagonists**:(rapid onset of action)
e.g. **Amiloride** and **Triamterene**: they inhibit Na+ influx by blocking Na^+-channels in the luminal membrane of DCT .

- They are given orally only.
- They do not cause hyperglycemia, hyperlipidemia or hyperuricemia and are not related to sulfonamides (no cross allergy and no carbonic anhydrase inhibition).

Potassium Sparing Diuretics

a) **Spironolactone** (Aldactone®) (25 – 50 mg/d)

- A synthetic steroid and structurally related to aldosterone.
- ↑ Ca2+ excretion via a direct effect on tubules
- Antiandrogenic effect: block androgen and estrogen receptor → loss of libido & gynecomastia in males and menstrual irregularities in female

- b) Eplerenone: A spironolactone analog with much greater selectivity for the mineralocorticoid (aldosterone) receptor and Less active on androgen and estrogen receptors

❖ Therapeutic uses:

1. **Hypertension :** used with thiazide or loop diuretics to compensate K+ loss and to potentiate their diuretic effect

   HCTZ 25 mg + Spironolactone 25 mg (Aldactazide®)

   HCTZ 50 mg + Amiloride 5mg (Moduretic®)

2. **Edematous conditions and resistant hypertension** due to Hyperaldosteronism: Spironolactone is of choice: more effective

❑ Primary hypersecretion (Conn's syndrome)

❑ Secondary hyperaldosteronism (heart failure, hepatic cirrhosis, nephrotic syndrome)

❑ Ascites: Accumulation of fluid in the abdominal cavity (ascites) is a common complication of hepatic cirrhosis.

Potassium Sparing Diuretics

3. **Alternative to thiazides and loop diuretics** when they are contraindicated in allergy to sulfonamides, D.M., and gout.

4. **Hypokalemia and Hypomagnesemia** due to thiazide or loop diuretics
   Triamterene and amiloride, are preferable to spironolactone

5. **Female hirsutism** (antiandrogenic use, spironolactone)

❖ Side effects & drug interaction:

a) **Hyperkalemia** especially in: renal impairment and drugs that inhibit renin release as β-blockers, NSAIDs, ARBs and ACE inhibitors.
b) **Metabolic acidosis**.
c) **Hypersensitivity** reactions as skin rash.
d) **CNS disturbances**: headache, drowsiness, confusion.
e) **Gynecomastia and impotence** in males due to androgen antagonism and irregular menstruation due to estrogen antagonism.
f) **Acute renal failure:** with combination of triamterene and indomethacin
g) **Kidney stones**: triamterene is only slightly soluble → precipitate in the urine → kidney stones

Carbonic Anhydrase Inhibitors

4. Carbonic Anhydrase Inhibitors (CAIs):

❖ Preparations:

- **Acetazolamide** Oral dose: 250-500 mg/day .
- **Dorzolamide** & **brinzolamide** topical eye drops.

❖ Mechanism and pharmacological effects:

- **In PCT**, Inhibits CA enzyme → prevent Na+ / H+ exchange → ↑ excretion of Na+ & HCO3− in urine
- **In the DCT**, Excess NaHCO3 will reach the late D.C.T. → ↑ exchange of Na+ & K+ ONLY → loss of K+ → loss of Na+ , K+ and HCO3− in urine (metabolic acidosis). → alkaline urine →↑ diuresis

❖ Therapeutic doses:

- They are weak diuretics (Not used as diuretic due to its low efficacy)

1. Glaucoma:

- ❑ CA inhibitors →↓ aqueous humor formation →↓intraocular pressure (IOP)
- ❑ **Acetazolamide** is used in acute congestive glaucoma by oral and IV routes.
- ❑ **Dorzolamide, brinzolamide** (topical eye drops), used in chronic simple glaucoma, without producing renal or systemic effects

Carbonic Anhydrase Inhibitors

2. Treatment of metabolic alkalosis.
3. Absence seizures (petit-mal epilepsy). By inducing acidosis.
4. To alkalinize the urine, as in treatment of acute toxicity of acidic drugs as salicylates and barbiturates.

❖ Side effects:

1. **Hypokalemia**
2. **metabolic acidosis** (↓diuretic efficacy of CA inhibitors
3. **Renal stones**: phosphate salts are relatively insoluble at alkaline pH)
4. **Allergy** & Cross-allergy with other sulfonamides
5. Avoid in patients with hepatic cirrhosis (↓ excretion of NH_4^+ in urine)

Osmotic Diuretics

5. Osmotic Diuretics:

- Non-absorbable agents able to bind with water → ↓reabsorption of H2O from PCT, descending loop of Henle and collecting duct.

❖ **Preparations:** (**mannitol, glycerol , isosorbide**)

❖ Mannitol:

- Strong osmotic diuretic. (given by IV infusion)
- Causes diarrhea if taken orally. (not absorbed)
- Not metabolized and is excreted by glomerular filtration within 30–60 min, without any important tubular reabsorption or secretion.

❖ **Mechanism of action**

- 20% Mannitol, on IV administration, →↑ osmolality of plasma → shift of fluid from the transcellular (e.g. aqueous humor, cerebral oedma)
- Mannitol is freely filtered at the glomerulus →↑ osmolality of tubular fluid→ Inhibits reabsorption of water →↑ urine flow → excessive water loss and hypernatremia

Osmotic Diuretics

❖ Therapeutic uses

1- As **a dehydrating agent** (withdrawal of fluids from tissue to plasma):

- ❑ Acute congestive glaucoma (↓ IOP)
- ❑ Acute rise intracranial pressure (↓ICP)
- ❑ Prophylactic against renal failure

2- **As a diuretic** ,It has rapid and potent diuretic action used in:

- ❑ Hypertensive crisis (emergency hypertension).
- ❑ Resistant edema.

❖ Side effect:

- **Dehydration, and Hypernatremia**
- **Headache, nausea, and vomiting**
- **Extracellular volume expansion**: mannitol is rapidly distributed in the extracellular compartment and extracts water from cells → expansion of the ECF and hyponatremia → complicate heart failure and pulmonary edema

Drugs used for Hypertension

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Introduction of hypertension

- **Hypertension is the Sustained elevation of arterial blood pressure > 140/90 mmHg.**
- **Normal BP** = systolic /diastolic = 120/80 mmHg
- **BP = CO × TPR**
  - ↑Cardiac output (CO) → ↑BP (mainly affect systolic blood pressure).
  - ↑Total Peripheral resistance (TPR) →↑ BP (affect mainly diastolic blood pressure).
  - Blood volume affect both systolic and diastolic blood pressure.

❖ Types and Causes (Etiology):

1. **Primary or essential:** =Idiopathic= there is no cause for hypertension, may be due to age, genetics, stress, weight, salty-diet, smoking.

2. **Secondary hypertension**: hypertension is caused by:
   - Diseases: renal failure, renal artery stenosis, Pheochromocytoma.
   - Drugs: (as corticosteroids, contraceptives, ergotamine, antidepressants, NSAIDs, decongestants or sympathomimetic drugs)
   - Pregnancy (pre-eclampsia)

Hypertension

Classification of blood pressure according to SBP/DBP reading		
Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal blood pressure	<120	<80
Prehypertension	120-139	80-89
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	180-209	110-119
Malignant or emergency	>210	>120

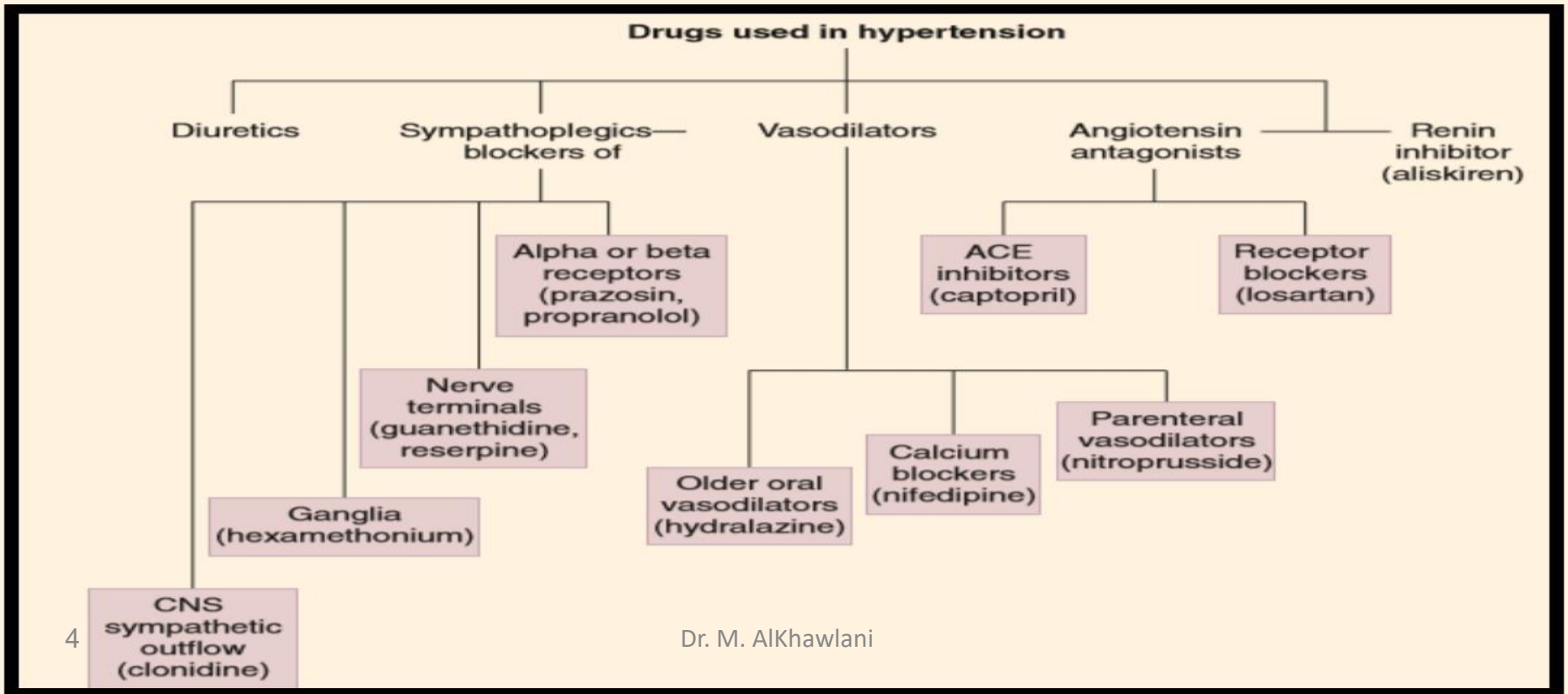
❖ **Complications of hypertension**:

1. Cerebral hemorrhage and stroke.
2. Retinopathy, blurred vision and glaucoma.
3. Epistaxis : nasal hemorrhage
4. Congestive heart failure
5. Coronary artery diseases (as angina)
6. Myocardial infarction.
7. Renal failure.

❖ Treatment of hypertension

A. Non- pharmacological therapy:

- Diet with low sodium and saturated fat.
- Weight reduction in obese.
- Avoid alcohol and smoking.
- Mild physical exercise.
- Stress reduction and relaxation therapies.
- Control blood glucose and lipids



Antihypertensive drugs

1. Angiotensin -Converting Enzyme Inhibitors (ACEIs)

❖ Preparation:

1. **Sulfhydryl-containing: Captopril, short acting**, 25- 50 mg,
2. **Non-SH -containing: long acting**
   a) Active drug: **Lisinopril**,; 5-20 mg, once/day
   b) Prodrugs: **Enalapril , Ramipril , Fosinopril, Quinapril**

❖ Pharmacokinetics:

1. All given orally after food except **captopril** is affected by presence of food, so it is better given on empty stomach (1-2 hours before meals).
2. **Enalapril** The only ACEI given IV → given IV in hypertensive emergency & **captopril** is given sublingual in emergency hypertension.
3. Pass placental barrier (teratogenic).
4. All undergo hepatic conversion to active metabolites, except **captopril** and **Lisinopril** (may be preferred in patients with severe hepatic impairment
5. All are excreted by the kidney except **fosinopril** excreted in bile

Angiotensin -Converting Enzyme Inhibitors(ACEIs)

❖ Mechanism of action:

Inhibit ACE →

- ↓ Synthesis of angiotensin II → (VD, ↓aldosterone & ↓ sympathetic stimulation)
- Prevent bradykinin breakdown → more VD (directly & by ↑ PGs)

❖ Pharmacological actions:

1. Mixed VD Arterial > Venous.
2. No reflux tachycardia. (↓ Baroreceptors reflux & ↓ sympathetic)
3. ↓ aldosterone synthesis and release → ↑ excretion of Na +and water in urine, and retention of K+ (hyperkalemia).
4. stimulates synthesis of bradykinin → V.D, dry cough.
5. Inhibition of vascular hypertrophy (narrowing) and cardiac hypertrophy (failure)
6. No change in blood glucose, no hyperuricemia, and no hyperlipidemia in contrast to other antihypertensive drugs as beta blockers and thiazides and loop diuretics.

Angiotensin -Converting Enzyme Inhibitors(ACEIs)

❖ Therapeutic uses:

1. **Hypertension** (HTN) especially in:
   a) Diabetic patients.
   b) Hypertensive with heart failure.
   c) High renin
2. **Congestive heart failure (CHF)** (decrease both pre-load and after-load).
3. **Post-Myocardial infarction** (**MI**), they prevent remodeling after myocardial infarction
4. **Diabetic nephropathy:** ACEI and ARBs are the preferred drugs in diabetic nephropathy

❖ Adverse effects:

1. **Postural hypotension (**1st dose effect) → started with a small dose and then gradually ↑
2. **Sulfhydryl containing drugs**: show **proteinuria**, **loss of taste**, **neutropenia** due to hypersensitivity reaction.
3. **Dry cough**, **urticaria** and **angioedema** (skin or mucous membrane swelling) due to ↑ BK & PG (give NSAIDs).



Urticaria



angioedema

Angiotensin -Converting Enzyme Inhibitors(ACEIs)

4. **Hyperkalemia**, especially if accompanied with K+ -retaining diuretics (e.g. Spironolactone, β-Blockers or in renal impairment).

5. Fetotoxicity (teratogenicity)

❖ Contraindications:

1. Pregnancy and lactation.
2. Bilateral renal artery stenosis.
3. Allergy.

❖ Drug interactions:

1. ACEIs + K-sparing diuretics→ dangerous hyperkaliemia.
2. ACEIs → retard the renal elimination of lithium (Li^+) → potentiate its toxicity
3. Chronic use of NSAIDs → Na+ and water retention (by inhibiting PG synthesis) → ↓ antihypertensive effect of ACEIs

Angiotensin Receptor Blockers (ARBs)

2. Angiotensin Receptor Blockers (ARBs)

❖ **Preparation:**

- **Losartan**, **Candesartan**, **Valsartan**, **Telmisartan**, **Irbesartan:** given orally once daily, except **Valsartan** twice a day

❖ **Mechanism of action:**

- Block AT-1 receptor → ↓ effects of Angio II. → more selective & complete inhibition of angiotensin action than ACEIs (More potent than ACEIs).
- Not interfere with bradykinin degradation → No dry cough , less angioedema
- Less hypersensitivity reactions (No sulphahydryl group)

❖ **Therapeutic uses:** similar to ACEIs

❖ **Adverse effects and contraindications :** as ACEIs but not cause dry cough, or angioedema

❖ **Drug interactions:** As ACEI,

- Should not be combined ACEIs + ARBs →↑ incidence of renal dysfunction and hyperkalemia

3. Direct renin inhibitors

As: Aliskiren

- Aliskiren, an orally active, long duration of action, used once daily
- Directly inhibits renin → inhibits renin activity and consequently the RAAS.
- It is used in treatment of hypertension, either alone (monotherapy) or combined with other antihypertensive agent.
- Should not combined with an ACE inhibitor or ARB.
- **Side effects:** diarrhea(at higher doses), cough and angioedema (less often than ACEIs)
- **Contraindicated:** during pregnancy

4. Calcium Channel Blockers (CCBs)

❖ Classification:

1. **Non-dihydropyridines:** **Verapamil & Diltiazem** → Heart > V.D.
2. **Dihydropyridines** (D.H.P.) →'V.D. > Heart:
   a) Long Acting: **Amlodipine.**
   b) Short Acting: **Nifedipine** , **Nicardipine & Nimodipine**.

❖ Pharmacokinetics

- All CCBs given orally and parenterally
- All are highly bound to plasma proteins (especially verapamil) and pass B.B.B.
- All metabolized in liver and excreted in urine

❖ Mechanism of action:

- Block L-type calcium channels in heart, blood vessels and smooth muscles → ↓ Ca influx. →
  - Cardiac inhibition → ↓ COP (**verapamil and diltiazem**).
  - Vasodilatation → ↓TPR (**Nifedipine**).
  - Relaxation of smooth muscles (as bronchi, GIT & uterus)
- Also CCBs → ↓ platelet aggregation
- Have little action on veins → not alter preload.

Calcium Channel Blockers (CCBs)

❖ Pharmacological actions:

- **Verapamil** acts mainly on the heart →cardiac suppression →↓contractility (↓cardiac work & oxygen consumption), bradycardia, ↓ AV conduction, ↓ Automaticity

- **Diltiazem** blocks Ca-channel in both cardiac and vascular smooth muscles. Also causes (-ve inotropic, -ve chronotropic and -ve dromotropic effects.

- **Nifedipine**: Act mainly on blood vessels (VD > ↓ heart):
  - Potent arteriodilators → ↓ after load. → ↓ TPR and ABP, with reflex tachycardia
  - Coronary vasodilatation. ↑ Renal blood flow
  - Headache, dizziness, and flushing also occur following V.D.

- Smooth muscle relaxation: CCBs relax smooth muscles of the bronchi, GIT, and ureters. .

❖ Therapeutic uses:

1. **HTN** (esp. D.H.P.): used also with patients old (aged ≥ 55yrs), low renin release, asthma, hyperlipidaemia, renal dysfunction or peripheral vascular disease).

Calcium Channel Blockers (CCBs)

2. **Angina pectoris and acute myocardial infarction (MI)**: Prophylaxis & Treatment (**Verapamil** in stable angina and **Nifedipine** in variant and unstable angina, due to its potent vasodilator effect.

3. **Cardiac arrhythmia**:
- **Verapamil & Diltiazem** are used in supraventricular arrhythmia
- **nifedipine** are contraindicated in tachyarrhythmias as they lead to reflex cardiac stimulation).

4. **Prophylaxis of migraine**. (as **Flunarizin & verapamil**)
5. **Premature labor**.
6. **Acute and chronic renal failure**.
7- Treatment of **cerebral ischemia** (nimodipine)

❖ **Side effect:**

1) **Verapamil & diltiazem** → bradycardia, hypotension, heart block, and HF, constipation

2) **Nifedipine** → reflex tachycardia, palpitation, headache and facial flushing and ankle edema

Calcium Channel Blockers (CCBs)

❖ Contraindications:

1. Hypotension.
2. **Verapamil** is contraindicated in: Bradycardia- heart Block-Congestive heart failure.
3. **Nifedipine** is contraindicated in tachyarrhythmias.

❖ Drug interactions

- Verapamil + β-blockers= severe bradycardia, AV block, and diminished contractility and may cause cardiac arrest.
- Verapamil + Nitrates = beneficial combination (verapamil prevents reflex tachycardia caused by nitrates).
- Nifedipine + β-blockers= beneficial combination (β-blockers prevent reflex tachycardia induced by nifedipine).
- Nifedipine + Nitrates= severe hypotension and reflex tachycardia.

Vasodilators

5. Vasodilators:

❖ Classification:

1- **Arteriodilators (V.D of arterial):** As **hydralazine, minoxidil, diazoxide, fenoldopam**
2- Venodilators as Nitrates
3- Mixed Dilators (Arterial and venous): As **sodium nitroprusside,** ACEI.

1- Hydralazine

- Long acting oral arteriolar vasodilator
- Metabolized in the liver by acetylation and Metabolites are excreted in urine

❖ Mechanism of action:

- Direct V.D. of arterioles → ↓ TPR (after-load) → ↓ ABP may act by NO release .
- Reflex sympathetic stimulation→ reflex tachycardia (add B-blocker).
- Also in kidney → ↑ renin → edema. (Add diuretics)

❖ Therapeutic uses:

- **HTN**: severe HTN (add B-blocker and diuretics) & HTN in pregnancy
- **CHF** in combination with nitrates,.

Vasodilators



Hydralazine SLE- like skin rash

❖ **Adverse effects:**

- Reflex tachycardia, edema (add B-blocker & diuretics)
- Headache, congestion, flushing, GI tract disturbances,
- Hypersensitivity reactions SLE-like syndrome. (Systemic Lupus erythromatosus)

❖ **Contraindications: in** Tachyarrhythmia.& angina pectoris

2- Minoxidil:

- A very potent, direct arteriodilator as hydralazine (oral arteriolar vasodilator)
- **M.O.A:** K+ -channel opener → efflux of K+ and hyperpolarization of smooth muscle of arterioles → V.D. of arterioles.

- **Used** orally for severe hypertension & heart failure unresponsive to other drugs (add B-blocker and diuretics). (Used also locally for alopecia as lotion or cream)

- **Side effects and contraindications**
- Tachycardia, edema and angina. Headache, congestion, flushing
- hypertrichosis.
- Hyperglycemia due to decrease insulin secretion



Minoxidil hypertrichosis

3- Diazoxide

- Direct arteriodilator acts as minoxidil (Activates K+-channels)
- Same structure as thiazide diuretics with no diuretic action
- Highly plasma protein binding
- It also inhibits insulin secretion from pancreas

❖ **Uses:**

- **Emergency HTN**, (given IV, and it used with β-blocker or diuretic)
- Hypoglycemia secondary to insulinoma.

- **Side effects :** Hyperglycemia, & Salt and water retention

4. Fenoldopam:

- Selective D1-agonist → V.D. of arterioles.
- Given by IV infusion.
- Used in emergency hypertension.
- Adverse effects: Reflex tachycardia- Headache-Flushing-Elevation of I.O.P.

Vasodilators

5. Sodium Nitroprusside

- Short acting IV drip mixed vasodilator (Arteriolar = Venular), (onset 1-3 min, Duration:3min)
- Metabolized in RBCs into cyanide (toxic metabolite) which is rapidly metabolized by rhodanase enzyme in the liver into thiocyanate (less toxic metabolite) which is excreted in urine.
- **Acts** by releasing of Nitric Oxide (NO) → ↑ Guanylate cyclase → ↓ Ca+ influx → V.D. of both arteriole and veins → ↓ TPR (after-load) and ↓ V.R (Pre-load) → ↓ ABP
  - inhibition of platelet aggregation.

❖ **Used:** Emergency hypertension. (as hypertensive encephalopathy) & Emergency heart failure because it has rapid action

❖ **Side effects:**

- Severe hypotension with large doses.
- Sudden stop → rebound hypertension.
- Accumulation of cyanide (prolong use) → arrhythmia & Death (treated by adding hydroxocoblamine (Vit B12) to bind with cyanide ions)
- Accumulation of thiocyanate → weakness, psychosis & convulsions. (treated by adding thiosulfate (sulfur donor) facilitates metabolism of cyanide

NB: - The drug is photosensitive so, must be made up fresh before each administration and covered it must to cover with foil.

6. Diuretics: Acts on Kidneys to ↑excretion of Na and H2O →↓ blood volume →↓BP

	Thiazide diuretic	Loop diuretics	Potassium sparing diuretics
Diuretic action	Moderate , slow and prolonged not effective with renal impairments	Rapid ,short duration ,effective in renal impairment	Weak & slow , not effective in renal impairment
Vasodilator effect	Potent & prolonged Hyperpolarization of vascular cell membrane due to opening of k channels &Decrease vascular Na , sensitivity to VCs	Short and mild -Increase synthesis of vasodilator PGs	-
Electrolytes	Loss of Na& K & Cl , H increase renal reabsorption of calcium	Loss of Na &CL & K , Ca &Mg & H	Loss of Na & Cl and prevention of K &H excretion
Blood pH	Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Metabolic actions	-Hyperglycemia & hyperlipidemia due to decrease insulin secretion as a result of k loss		
Uric acid	Hyperuricemia (gout) due to competition with uric acid at site of excretion		
Uses	Long term treatment of mild & moderate , low renin hypertension: Chlorthalidone	-Emergency hypertension IV Furosemide -Resistant hypertension : oral furosemide	In combination with other diuretics to prevent k loss or singly if there allergy to other diuretics
Preparations	Short acting (hydrochlorothiazide,) . long acting(chlorthalidone), Metazolone effective in renal impairment	Furosemide & ethacrynic acid , bumetanide	Aldosterone antagonists spironolactone
Side effects	Tolerance due to activation of renin angiotensin system, hypo(kalemia & natremia, volemia) , hyper(glycemia , lipidemia , urecemia) ,alkalosis		Hyperkalemia , decrease release of sex hormones

7. Sympathetic Depressants:

1. Alpha blockers:

1- Non-selective α1 & α2-blockers: phenoxybenzamine & Phentolamine

2- Selective α1-blockers: Prazosin, terazosin & doxazosin

- Selective α1 –blockers are better than non –selective (less reflex tachycardia)

❖ **Mechanism of action** selective α1 receptor blockers:

- ↓ BP by ↓ block of α1 receptor on blood vessels → dilatation of arteries and veins → ↓ TPR → hypotension.
- No (or minimal) tachycardia

❖ **Therapeutic uses:**

- Selective α1 –blockers: for **mild to moderate hypertension** (with diuretics or β-blockers) and preferred in cases of **benign prostatic hypertrophy** (BPH) and **peripheral vascular diseases**
- Non selective α –blockers: only used to treat HTN with pheochromocytoma

❖ **Side effects**:

- Postural hypotension (first dose effect), flushing, nasal obstruction due to VD and congestion of nasal vessels. Na+ & H20 retention

Sympathetic Depressants

2. β- blockers:

❖ Preparation:

1- **Non- selective β- blockers (β1 & β2)**: **Propranolol, pindolol**

2- Selective B1-blockers: Atenolol, Metoprolol, Bisoprolol.

- Given orally and parenterally

❖ Mechanism of action:

- Block β1 receptors → ↓ cardiac output & ↓ renin release
- Block β2 receptors → ↓NE release and Resetting of baroreceptors to lower levels

Advantages:

- Prevent tachycardia induced by hypotensive drugs (B1 receptor blockade)
- Decreases cardiac work (Cardia-protective).
- Relieve of anxiety only lipophilic B blockers (B2 receptor blockade)

❖ Therapeutic uses:

- In **Mild & Moderate Hypertension** in cases of
  1- High renin hypertension.
  2- Anxiety and exercise induced hypertension
  3- Hypertension in young persons & in patients with angina

❖ Side effects:

- Bradycardia, heart block failure. & Hypotension, Bronchoconstriction, hyperlipidemia, hypoglycemia &hyperkalemia .
- Sudden stop causes rebound hypertension and tachycardia due to upregulation of beta receptors (Tolerance).

❖ Contraindications:

- Bronchial asthma, COPD, Peripheral vascular diseases, as vasospastic (variant) angina
- Diabetes mellitus (DM

3. α1 & β- blockers (Vasodilator B-'Blockers): As - Labetolol & Carvedilol

- Blocks β -and α1-receptors →↓ both COP and TPR. → ↓ ABP
- It causes V.D. and hypotension without reflex tachycardia.

- **Labetalol** is used in **HTN** with emergency**,** pheochromocytoma and during pregnancy.

- **Carvedilol** is used in the treatment of **heart failure** and **HTN**.

4. Adrenergic neuronal blockers: Guanethidine, Clonidine, Reserpine, Alpha methyl dopa

	Guanthidine	Clonidine	Reserpine	Alpha methyl dopa
Mechanism of action	Decrease NE uptake I Inhibition of NE release	Decrease NE release by stimulation of presynaptic α_2 receptors	Decrease NE uptake III -Inhibition of NE storage	Decrease NE synthesis
Cardio-vascular effect	IV causes initial VC , tachycardia and hypertension followed by VD , bradycardia , hypotension more diastolic than systolic ,Oral causes slow VD , bradycardia and hypotension Initial inhibition of NE storage followed by metabolism Initial stimulation of post then presynaptic α_2 receptors		Rapid prolonged VD, hypotesion , bradycardia	Slow prolonged VD, hypotesion , bradycardia
CNS	No effect because it does not pass BBB	Depression (antianxiey , sedative , hypnotic , analgesic , central skeletal muscle relaxant)		
Renal function	Salt and water retention due to decrease renal blood flow as a result of hypotension and bradycardia. This leads to tolerance to their antihypertensive effect			
GIT &UT	Stimulation leading to diarrhea , increase HCL secretion , peptic ulcer			
Anti-hypertensive effect	← In resistant severe hypertension in combination with diuretics to prevent tolerance →			
	Contraindicated in emergency hypertension because they cause initial hypertension		Emergency hypertension	hypertension during Pregnancy
Contra-indications	Heart failure (cardiac depressant) ,bronchial asthma , peptic ulcer (bronchospasm and increase HCl secretion due to parasympathetic predominance) , pheochromocytoma (do not affect epinephrine release from adrenal gland).			
Side effects	Bradycardia , diarrhea , peptic ulcer , bronchospasm , sedation , salt and water retension , Postural hypotension (the least with α methyl dopa) , reserpine and alpha methyl dopa causes parkinsonism & sexual dysfunction & hyperprolactinemia (guanthidine does not pass BBB)			

Dr. M. Alkhawlani

Antihypertensive drugs

❖ **Drug therapy:**

- **Initial monotherapy with one of the following drugs:**
  - Angiotensin-converting enzyme inhibitors (ACEIs)
  - Beta-blockers
  - Calcium channel blockers
  - Diuretics

- **Double therapy for resistance cases with 2 drugs:**
  - Beta-blockers + diuretics
  - Beta-blockers + ACEI
  - Beta-blockers + DHP of CCB
  - ACEI + diuretics

- **Triple therapy for resistance cases with 2 drugs**
  - Beta-blockers + loop diuretics + vasodilators
  - If Beta blockers are contraindicated, they should be replaced by clonidine or centrally acting antihypertensive drugs

Choice of Antihypertensive

	Drug used	Drugs C.I
- HTN + heart failure:	ACEI or ARB	C.C.B
- HTN + diabetes:	ACEI or ARB	B-blockers, Diazoxid thiazide or loop diuretics
- HTN+ Angina	B blockers or C.C.B	Hydralazine, Minoxidal
- HTN+ renal diseases	Loop diuretic, C.C.B	Thiazide diuretics, ACEI. ARB
- HTN + bronchial asthma:	C.C.B.	B blockers , ACEI
- HTN+ Elderly	Thiazide, C.C.B	
- HTN + Hyperlipidemia	C.C.B, ACEI, ARB	B-Blocker, Diuretics
- HTN+ PVD	α-Blocker, ACEI, CCB	B-Blocker
- **HTN+ Pregnancy** - Early - Labor (eclampsia)	α methyl dopa (Choice) Nifedipine(, labetalol hydralazine, labetalol	ACEI, ARB, B-Blocker

Choice of the antihypertensive drugs:

Clinical condition	Best choice
Starting therapy for non-complicated essential hypertension	Patient <55 years old: ACE inhibitors Patient >55 years old: CCBs If not adequate, add thiazide or beta blockers.
Hypertension of pregnancy	α-methyldopa Labetalol – Nifedipine - Hydralazine
Hypertension in a diabetic patient with diabetic nephropathy (proteinuria)	ACE inhibitors
Hypertension with chronic kidney disease	S. creatinine <3 mg/dl: ACEIs S. creatinine >3 mg/dl: CCBs
Hypertension with CHF	ACE inhibitors - diuretics
Hypertension with bronchial asthma	CCBs
Hypertension with angina	CCBs - beta-blockers
Hypertension with thyrotoxicosis, sympathetic overactivity, arrhythmia, or, HOCM	Beta-blockers
Hypertension with BPH	α1 blockers
Primary pulmonary hypertension	Endothelin receptor antagonists

Drugs used for Angina Pectoris (Ischemic Heart Diseases)

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Angina Pectoris

- Sudden chest pain due to transient myocardium ischemia.

- The cardiac ischemia is due to the imbalance between:
  - Cardiac work (oxygen need) and Coronary arteries flow (oxygen supply)
  - Results when the Cardiac work (oxygen need) is increased while the narrow coronary arteries fail to dilate (↓oxygen supply) → angina pain.

NB: Angina Pectoris also called **coronary heart disease** (CHD) or **coronary artery disease** (CAD) or **Ischemic heart disease** (IHD).

❖ Types of angina:

1. Stable Angina (Effort, Exertional, Classic):

a) Most common type.

b) Pain occur during exercise due to atherosclerosis → Coronary lumen is narrowed & fixed and fail to dilate

c) Treatment by: Rest or ↓ Cardiac work.

Angina Pectoris

2. Variant (Prinzmetal, Vasospastic) Angina:

a) Pain occur at rest due to sudden spasm Of coronary vessels (Coronary V. C)

b) Treatment by Coronary V.D.

3. Unstable Angina (Pre-infarction):

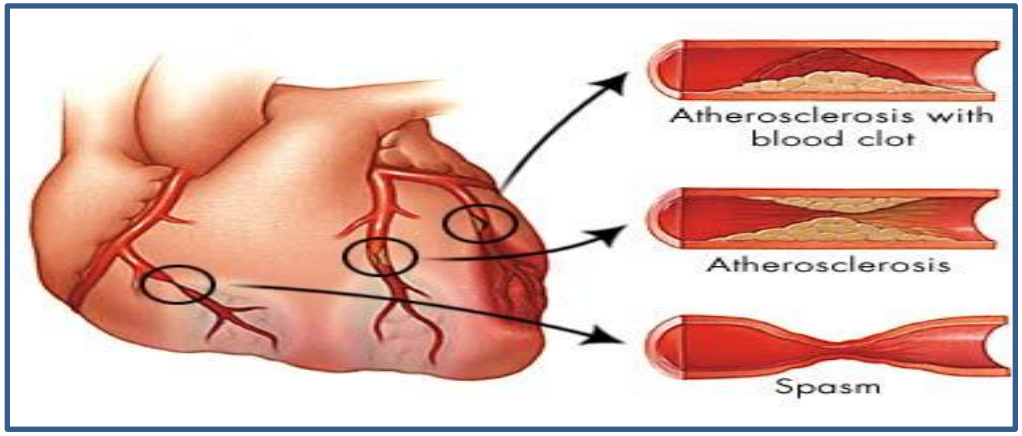
a) Pain occurs on mild exertion then on rest.

b) Due to partial obstruction of coronary artery by small platelet thrombus or atherosclerotic plaque (atherosclerotic with blood clot).

c) Treatment: Hospitalization+ Coronary V.D. +↓Cardiac work + Anti-thrombotics.

❖ Complications of Angina Pectoris:

- May lead to **myocardial infarction.** (Due to complete coronary obstruction → necrosis of part of the heart and sudden cardiac death.



Angina Pectoris

- **Antianginal drugs**: either ↑ oxygen supply or ↓ oxygen demand (need) or both

1. **↓ O2 demand:** ↓ cardiac work **:**
   - ↓ heart rate and contractility (β- blockers and CCBs)
   - ↓ preload (nitrates) & ↓ Afterload (CCBs, K channels openers)
2. **↑ coronary O2 supply:**
   - Coronary vasodilatation (CCBs/ nitrates).
   - Prevent thrombus formation (antiplatelet drugs) & Lipid lowering drugs (Statins)

❑ Anti-anginal drugs include:

1. Nitrites & Nitrates: Both → Coronary V.D. + ↓ Cardiac work.
2. **CCB**: Both → Coronary V.D. + ↓ Cardiac work.
3. **B-Blockers** → ↓ Cardiac work.

4. **Newer antianginal drugs**:
   - Ranolazine and Ivabradine → ↓ Cardiac work.
   - Nicorandil: Both → Coronary V.D. + ↓ Cardiac work.

5. **Antiplatelet drugs:** aspirin & clopidogrel. & **Lipid lowering drugs**: **statins**.

1. Organic Nitrates (Nitrates and Nitrites):

❖ Preparation:

1. Short acting:

- Nitroglycerin, sublingual (0.5 mg /5 min., Max 3 doses) - Onset of action: 1-3 min. Duration 10- 30 min.

2. Long – acting:

- Nitroglycerin, GTN: Oral SR capsules, Transdermal patches- Onset: 30 min, Duration: 4-8 h, 24 h.
- Isosorbide Dinitrate (ISDN). SL (2.5-10 mg, Onset: 2-5 min, Duration 2- 4 h & Oral tablet (5-40 mg TID, Onset: 15-40 min, Duration 2- 6 h)
- Isosorbide Mononitrate. Oral tablet (20 - 40 mg BID, Onset: 30-60 min, Duration 2- 6 h) & S R Capsules (60-120 mg once daily, Onset: 30-60 min, Duration 8- 12 h)

Angina Pectoris

❖ Pharmacokinetics:

- Absorbed from buccal mucosa, skin, GI tract (lipid- soluble).
- All nitrates except **ISMN** undergo - first-pass metabolism → ↓ oral bioavailability → can be overcome by:

  - **Sublingual tablets & spray**: rapid onset/ short-action: 2min /30 min for nitroglycerin & 5 min / l h for ISDN → 1st choice for acute attack & for immediate prophylaxis.

  - **Transdermal route:** delayed onset/ longest duration → used for long term prophylaxis & CHF

- Excreted as Glucuronide conjugates. denitrated by a **glutathione S - transferase** and a mitochondrial **aldehyde dehydrogenase** → excreted, in urine as glucuronide derivatives

❖ Mechanism of action:

- Nitrates rapidly denitrated on vessel wall by Glutathione transferase enzyme (consuming S-H group) → Release of Nitric Oxide → ↑ guanyl cyclase → ↑ cGMP:
  - Dephosphorylation of myosin light chain → smooth muscle relaxation
  - ↓ platelets aggregation.

- Also ↑intracellular cGMP →↓ Ca2+ entry→ relaxation of vascular smooth muscle → coronary V.D (e.g. vasodilation; selective venodilators).

Angina Pectoris

❖ Pharmacological actions:

❖ Nitrate relive anginal pain by ↓ the O2 demand and↑ the O2 supply to the myocardium

- ↓ **O2 demand (relieve pain):** ↓cardiac work

  - **Venodilatation** ,→ ↓ venous return → ↓ pre-load → ↓cardiac work.→ ↓ myocardial O2 demand, Venodilatation → postural hypotension
  - **Arteriolar vasodilatation** (in large dose) → ↓ after-load → ↓cardiac work.→ ↓O2 demand
  - VD of arteries → flushing of the face, headache. Reflex tachycardia (in high dose)

- ↑ **O2 supply**: ↑ coronary blood flow
  - VD of large epicardial coronary arteries.
  - VD of collaterals.
  - Redistribution of blood to subendocardial ischemic areas

- **Antiplatelet activity** contributes to their antianginal effect (in unstable angina).
- **Blood**: Methemoglobinemia in high doses due to oxidation of Hb into metHb
- **On other smooth muscles**: relaxes of smooth muscles of the bronchi, biliary tract, etc.

Angina Pectoris

❖ Therapeutic uses:

1. **All types of angina** (stable, variant, and unstable)

- **Stable angina:** ↓ preload & ↓ afterload →↓ cardiac work →↓ heart O2 requirements
- **Vasospastic angina**: dilate median sized epicardial arteries → ↑ the O2 supply
- **Unstable angina** (acute coronary syndrome): ↓ heart O2 need, coronary V.D. and antiplatelet effect.
- **Myocardial infarction**: ↓ pre-load and antiplatelet effect and redistribution of coronary flow to ischemic area.

NB: given S.L. or by buccal spray in acute attacks and immediate prophylaxis,

- given orally, as skin ointment, and as transdermal patch for long-term prophylaxis.
- Nitroglycerin is given by IV infusion in unstable angina.
- **ISMN** is preferred over ISDN for chronic prophylaxis of angina (b/c longer duration of action, and high oral bioavailability)

2. Congestive heart failure (CHF)

3- Other uses:-It may be used in treatment of biliary spasm

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4- Nitrites are used in **cyanide poisoning** because they cause methemoglobinemia. as amyl nitrite (inhalation) and sodium nitrite (IV).

❖ Adverse effects:

1. **Postural hypotension**, **reflex tachycardia** (adding B -blockers or verapamil to nitrates), **headache, skin flushing**.
2. **Cyanosis (**non functioning methemoglobin, methemogobinemia).
3. **Sudden withdrawal:** cause angina and myocardial infarction.
4. **Rapid Tolerance with chronic use (**due to depletion SH group required for de-nitration of nitrates & VC due to activation of adrenergic & renin-angiotensin systems).
5. Nitrates used as preservatives may cause **cancer** due to formation of nitrosamine by combination with amino acids
6. **Monday diseases**: workers on nitrate industry show **headache** on first day after weakly holiday which is relieved on the following day due to nitrate tolerance

❖ Drug Interactions:

1. Nitrates+ B-blockers (propranolol) = beneficial combination.
2. Nitrates+ Verapamil =beneficial combination.
3. Nitrates+ Nifedipine =unfavorable combination.
4. Nitrates+ Sildenafil (Viagra®)) = very dangerous combination causes severe VD , hypotension , tachycardia and fatal arrhythmias. sildenafil inhibition of phosphodiesterase 5 leading to increased intracellular c-GMP.

❖ Precautions during nitrate therapy

- They should be protected from light and moisture.
- Administrated of drug on sitting position to prevent fainting as a result of postural hypotension (syncope occurs).
- Maximum of 3 tablets in 15 mins (5mins apart), If pain not relieved, patient is referred to hospital.
- To avoid tolerance; allow a nitrate free period for 8 hrs/day.
- Nitrates should not be sudden stopped to avoid precipitation of angina.

2. Nicorandil: orally VD, a new organic nitrate with vasodilator properties. (5 – 30 mg BID)

- Nicorandil: Both → Coronary V.D. + ↓ Cardiac work.
- Nicorandil→ opens ATP-dependent K+ channels → K+ efflux→ hyperpolarization of vascular smooth muscle cell→ arterial vasodilation
- Also acts as NO donor →↑ cGMP → relaxes blood vessels
- NO donor , K channel opener → veno & arterial dilation . It has similar effects to nitrates
- ↑Coronary flow by dilatation of epicardial conducting vessels
- Useful in Angina & Heart failure. Used also as add-on therapy to control symptoms of refracted angina
- No tolerance.

❖ **Side effects:**- Flushing, hypotension, reflex tachycardia, headache, dizziness.

3. β-Blockers:

❖ Preparations :

- All B-Blockers (selective or non-selective) are effective in angina pectoris
- **Better use** → B1-selective blockers with no intrinsic sympathomimetic effects (I.S.A).
- **Non-selective:** Propranolol & Nadolol.
- **Selective:** B1-Blockers e.g. Atenolol, Metoprolol & Bisoprolol.
- **Vaso-dilator** B-Blockers e.g. Carvedilol

❖ Mechanism of action:

- ↓ **O2 demand (relieve pain): ↓cardiac work**
  - ↓ HR, and ↓contractility →↓ cardiac work & blood pressure → ↓ myocardial O2 demand at rest and during exercise.
- ↑ **O2 supply**: ↑ coronary blood flow
  - ↓ heart rate →↑ diastolic perfusion time →↑ coronary perfusion.
- Prevent tachycardia induced by Anxiety & Exercise and by drugs (Nitrates & Nifedipine).

Angina Pectoris

❖ Therapeutic uses:

- Useful in Prophylaxis of Angina Pectoris:

1. 1st line treatment in Stable angina. Better use cardia-selective B1-blockers
2. 2nd line treatment of unstable angina (acute coronary syndrome), acute myocardial infarction not associated with severe hypotension or pulmonary congestion or decompensated heart failure).
3. Can be combined with Nitrates & Nifedipine to prevent tachycardia induced.

❖ Side effects:

- **B1 blockade**: Bradycardia, heart block and Overdose causes severe hypotension.
- **Non-selective B-Blocker:** Bronchospasm, silent hypoglycemia, cold extremities
- Sudden withdrawal causes rebound hypertension and tachycardia

❖ Contraindications:

- Vasospastic angina: coronary spasm (Non-selective B-Blockers), Bronchial asthma, HF, Peripheral vascular diseases, Diabetes mellitus (DM),
- β-Blockers with intrinsic sympathomimetic activity (I.S.A) as pindolol, acebutalol
- NOT combined with Verapamil → Severe cardiac inhibition

4. Calcium Channel Blockers (CCBs):

❖ Preparation:

1. **Cardio-specific (non D.H.P):** ↓ Heart > V.D: Verapamil & Diltiazem

2. **Vasculo-selective (D.H.P.):** V.D. > ↓ Heart: Nifedipine (Short-acting) & Amlodipine (Long-acting)

❖ Mechanism of action:

- **↓ O2 demand: ↓cardiac work**

  - ↓ HR, and ↓contractility →↓ cardiac work & blood pressure → ↓ myocardial O2 demand

  & Dilatation of median sized epicardial coronary vessels (Verapamil & Diltiazem).

- **↑ O2 supply**: ↑ coronary blood flow

  - Dilatation of median sized epicardial coronary arteries, improving coronary perfusion (Nifedipine & amlodipine). Cause hypotension and reflex tachycardia .

- **↓ Platelet aggregation.**

- **Smooth muscle relaxation**: Bronchial, Biliary, GIT, Urinary & Uterine.

Angina Pectoris

❖ Therapeutic uses:

1- **All types of angina** (↓ Cardiac Work & Coronary VD):

- 2nd line treatment in stable angina & 1st line drug in treatment of vasospastic angina

a) verapamil & diltiazem: specially in Angina + Cardiac arrhythmia.

b) Nifedipine & amlodipine: specially if angina + HTN, B.A, D.M., P.V.D

2- **Acute myocardial infarction**. (↓ cardiac work and O2 consumption)

3. **Hypertension:** DHPs -verapamil –diltiazem (long acting DHPs induce smooth hypotension with less reflex tachycardia → preferred to short acting DHPs).

4. **Supra ventricular arrhythmia**: (verapamil)

5. Peripheral vascular diseases- migraine prophylaxis- prevent premature labour

❖ Side effects:

1) Verapamil & diltiazem → bradycardia, hypotension, atria-ventricular block, and HF, constipation → should not be used in patients with HF or in those taking β-blockers.
2) Nifedipine→ reflex tachycardia → worsen angina, palpitation, headache and facial flushing and ankle edema

❖ Contraindications:

1. Hypotension.
2. Verapamil is contraindicated in: Bradycardia- AV Block-Congestive heart failure.
3. Nifedipine is contraindicated in tachyarrhythmias.

❖ Drug interactions:

- CCBs especially verapamil displace digitalis from plasma proteins.
- Verapamil + β-blockers= severe bradycardia.
- Verapamil + Nitrates = beneficial combination (verapamil prevents reflex tachycardia caused by nitrates).
- Nifedipine + β-blockers= beneficial combination (β-blockers prevent reflex tachycardia induced by nifedipine).
- Nifedipine + Nitrates or Sildenafil = severe hypotension and reflex tachycardia.
- Nifedipine + Verapamil = beneficial combination (Verapamil prevent reflex tachycardia induced by nifedipine).

5. Other antianginal agents (Newer Antianginal Drugs)

1. **Ranolazine:** 500-1000mg BID

- Act by block of late Na channel that facilitates calcium entry via the sodium-calcium exchanger →↓ in intracellular calcium concentration →↓diastolic tension, cardiac contractility, cardiac work & oxygen demand.
- Ranolazine has antianginal (stable angina) as well as antiarrhythmic properties.
- It is used as adjuvant with or alternative to B blockers or nitrates if there is poor response or intolerance

➢ **Side effects**: headache, dizziness, constipation and nausea; ↑ QT → contraindicated in patients with long QT syndrome or taking drugs which↑ QT

2. **Ivabradine:** 5-7.5 mg BID

- Selectively inhibits the sinoatrial pacemaker →↓ HR and myocardial oxygen demand, similar in efficacy to B-blocker and CCBs.
- It is used in supraventricular arrhythmia, Systolic heart failure, stable angina as alternative to B- blockers if there is contraindication to use of B-blockers

- **Side effect** are bradycardia, heart block, increase brightness of visual field
- Contraindicated with CCBs (inhibits metabolism of CCBs).

Angina Pectoris

❖ Antiplatelet Drugs:

- They inhibit platelet aggregation & ↓the incidence of MI and sudden cardiac death

  - They include:

1. Aspirin (ASA) (pediatric dose= 75-150 mg /day). They inhibit TXA2 synthesis.
2. Ticlopidine and Clopidogrel: inhibit ADP-dependent platelet aggregation. Represents a suitable alternative antiplatelet agent to prevent MI and death in chronic stable angina patients unable to take ASA.

❖ Antihyperlipidemic drugs

- **Statins**: such as: Simvastatin, Atorvastatin
- In addition to cholesterol-lowering properties, statins also have antithrombotic, antiinflammatory, antiproliferative properties and restoring normal endothelial function of the vessel wall.
- Orally, used in combination with other anti-anginal drugs to prevent atherosclerosis or thrombus formation → prophylaxis of angina

Angina Pectoris

Anti-anginal drugs

1) Acute attack	Short acting nitrate	Nitroglycerine –isosorbide dinitrate (sublingual).
2) Maintenance therapy for chronic angina	B-Blocker (1st choice). For stable angina	Propranolol, metoprolol, atenolol
	- CCBs alternatives if B-Blocker are CI (e.g. in. asthmatics). - CCBs are 1st choice in vasospastic angina	Non- DHP (verapamil, diltiazem) DHP (nifedipine SR, felodipine, amlodipine)
3) Third-line antianginal drugs	Long acting oral nitrate	Isosorbide mononitrate (ISMN
	K - channel opener	Nicorandil
	The newer agents	Ranolazine, Ivabradine
4) Secondary prevention	Antiplatelet agents(low-dose aspirin, clopidogrel), ACE inhibitors (ACEIs), Statins	

Dr. M. Al Khawlani

C) **Unstable Angina**

1. Hospitalization.
2. Nitroglycerine S.L or I.V. then Oral & Transdermal
3. Nifedipine + Cardia-selective B-Blocker without I.S.A. e.g. Atenolol
4. antiplatelet agents, anticoagulants as: Aspirin & Heparin and statins
5. Coronary Artery Reperfusion Surgery.

❖ **Choice of Treatment with other disease:**

Patient	Useful Drugs	Drugs Contraindicated
1- Variant Angina	CCB & Nitrate	Non-selective B-Blockers
2- Angina +B.A., P.V.D. or D.M	CCB (D.H.P) & Nitrate	Non-selective B-Blockers
3- Angina+ H.B. or H. F.	Nitrates & Nifedipine	B-Blockers & Verapamil

Drug therapy of congestive heart failure

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Congestive heart failure

- **Congestive heart failure** is a clinical syndrome in which the heart is unable to pump an adequate supply of blood to maintain adequate tissue perfusion.

❖ Clinical picture of heart failure

1. **Congestive symptoms** due to ↑ preload and inability of the heart to receive all venous blood during diastole. They include:
   - Pulmonary congestion → severe dyspnea.
   - Edema in abdominal cavity (ascitis)
   - Generalized edema starting from lower limb and progresses upwards.

2. **Ischemic symptoms** due to ↓ cardiac output → ↓ blood flow to most organs namely:
   - Brain ischemia → confusion and intermittent respiration
   - Cardiac ischemia → chest pain (angina).
   - Muscle ischemia → pain during muscular exercise (claudication).

❖ Degrees of heart failure

- **Class 1** Symptoms occur at more than ordinary activity.
- **Class II** is characterized by slight limitation of ordinary activities due to fatigue and palpitation
- **Class III** fatigue, palpitation in ordinary activities.
- **Class IV** Fatigue and palpitation at less than ordinary activities

Congestive heart failure

Management of Heart Failure

		I. ↓ Preload Improve congestion	II. ↓ Afterload Improve low COP	III. ↑Contractility Improve low COP & congestion	IV. Protect Heart &/or restore its function
Lines of Treatment		• Salt & Fluid restriction. • Diuretics. • Venodilators	• Physical/ mental rest. • Arteriodilators	• Positive inotropics.	• β-blockers • Aldosterone antagonists
Drugs Used	**For CHF**	• Loop diuretics • ACEIs. • ARBs. • Nitrates	• ACEIs • ARBs. • Hydralazine	• Digoxin	• β-blockers Carvedilol Bisoprolol Metoprolol • Spironolactone • Eplerenone
	For AHF	• Loop diuretics • Nitrates. • Nitroprusside	• Nitroprusside	• Dopamine. • Dobutamine. • Inamrinone.	

Drug used for congestive heart failure

1. Inhibitors of renin angiotensin system

- **ACEI:** Captopril, enalapril, Lisinopril.
- **ARB**: Losartan, valsartan.

❖ Mechanism of action in heart failure:

- Inhibit conversion of angiotensin-I to angiotensin-II resulting in the following:

- ↓ in aldosterone production → ↓ in sodium and water retention → ↓ preload
- Vasodilatation of:
  - venodilataion → ↓ preload (↓ venous congestion).
  - arterial vasodilatation → ↓ after load (↑ COP) → improved tissue perfusion.
- Reversion of cardiac remodeling

❖ Therapeutic uses: They are the initial drug of choice in all classes of heart failure.

❖ Side effects:

1. 1st dose hypotension → start with low dose at evening. (1/4 of antihypertensive dose)
2. ACEI cause dry cough due to activation of bradykinin

Drug used for congestive heart failure

- **Angiotensin receptor neprilysin inhibitor (ARNI):** Sacubitril/valsartan
  - Combination of the ARB“ valsartan“ & "sacubitril an inhibitor of neprilysin enzyme that degrades atrial natriuretic peptide"ANP → Na excretion, diuresis, vasodilation.
  - Used in stead of ACEI or ARB in patients with classII- IV heart failure, with persistent symptoms

Drug used for congestive heart failure

2. B blockers

❖ **Preparations of choice:** Carvedilol (V.D. +Anti-oxidant) > metoprolol > Bisoprolol.

❖ **Mechanism of action**:

- Block the Sympathetic and Renin angiotensin system activation in HF → protect the heart against the remodeling and apoptosis.

❖ **Therapeutic uses**:

- They are useful in asymptomatic class 1 &2 heart failure, heart failure with severe tachycardia, heart failure in anxious patient.
- Reduces hospitalization and decreases mortality when added to ACEIs & diuretics in patients with mild-to-moderate heart failure.

❖ **Side effect**:

1. They are contraindicated in severe cases of congestive heart failure because they aggravate both congestive and ischemic symptoms of heart failure.
2. They are unsuitable for patient with diabetes mellitus (mask the symptoms of hypoglycemia), bronchial asthma (they produce bronchospasm).

Drug used for congestive heart failure

3. Vasodilators (Nitrates and hydralazine)

- **Mixed arteriolar and venodilators**: ACE inhibitors, ARBs, sodium nitroprusside (reduce both preload and afterload).
- **Venodilatory effect**: Nitrates (reduce preload, also have some effect on arterioles).
- **Arteriolar dilating effect**: Hydralazine (reduces afterload).

- Nitrates and hydralazine have complementary hemodynamic actions:
  - Nitrates are primarily venodilators, →↓ preload.
  - Hydralazine is a direct arterial dilator →↓ systemic vascular resistance and afterload.
- The combination →↓ mortality and hospitalizations for patients with HF in moderate to severe HF.
- The combination is also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs due to any contraindication**.**
- A fixed-dose combination product (isosorbide dintrate 20 mg and hydralazine 37.5 mg).

- IV nitroglycerine is used in severe acute of class 4 heart failure →↓ preload by predominant venodilatation.

- Sodium nitroprusside is powerful short acting parenterally vasodilator. Mixed VD → ↓ Preload & Afterload →↑ C.O.P & ↓ Congestion.

Drug used for congestive heart failure

4. Diuretics

❖ Preparations:

- Loop (furosemide) 1st choice especially in refractory or pulmonary edema
- Thiazide (hydrochlorothiazide, chlorthalidone): used in mild-to-moderate cardiac failure
- They are used in combination with potassium sparing diuretics (spironolactone) to prevent potassium loss by loop and thiazide diuretics.

❖ Mechanism of action in heart failure:

- Diuretics are given for fluid control in cases with symptomatic HF & fluid Retention →↓ blood volume and vasodilator effect →↓ preload and afterload. →↓ Pulmonary congestive symptoms &↓ Peripheral (ankle) edema in patients with moderate class 3 and severe class 4 congestive heart failure.

❖ Disadvantages and side effects

- They may aggravate ischemic symptoms of heart failure by ↓blood volume.
- Loop and thiazide → loss of potassium→ hyperglycemia and hyperlipidemia and cardiac arrhythmia → aggravate the toxicity of digoxin due to potassium loss.
- Loop and thiazide → aggravate hypotensive effect of inhibitors of renin angiotensin system due to decreasing blood volume.
- Spironolactone → hyperkalemia, gynecomastia. It is contraindicated with inhibitors of renin angiotensin system

Drug used for congestive heart failure

5. Positive Inotropic Drugs (Myocardial Stimulants)

a) To increase myocardial contractility it is essential to increase free Ca2+ inside cardiac cells.
b) Mechanisms to increase free Ca2+ include:
- Increasing intracellular c-AMP by:

1. β1-agonist (dopamine, dobutamine), → activation of adenylyl cyclase → ↑c-AMP.
2. Inhibition of phosphodiesterase (PDE) by Methyl xanthines (as Aminophylline) and Bipyridines (as Amrinone and Milrinone).

- ↑ intracellular Na+ by inhibition of Na+/K+ ATPase by Cardiac Glycosides (Digitalis)

1. Cardiac glycosides (digitalis derivatives)

Source: plants

1. Digitalis purpurea leaves → Digitoxin.
2. Digitalis lanata leaves → Digitoxin & Digoxin
3. Strophanthus gratus seeds→ Ouabain**.**

Chemical structure: each molecule is composed of:

1. Non-sugar part (aglycone) formed of a steroid nucleus; it is responsible for the pharmacodynamics properties.

2. Sugar part (glycone) which is responsible for the degree of lipid solubility and accordingly the pharmacokinetic properties.

Cardiac glycosides (digitalis derivatives)

❖ Pharmacokinetic:

Pharmacokinetic parameter:	Digoxin	Digitoxin
oral Absorption:	Moderate.	Almost complete.
Oral bioavailability	75%	90%
Route of administration:	Orally and IV.	Orally only
Plasma protein binding	25%	90%
Fate:	Mainly excreted unchanged in urine (avoided in renal Diseases).	Mainly metabolized by HME (avoided in Liver diseases).
Excretion	Renal (90%)	Hepatic (90%)
Accumulation (especially in cardiac and skeletal muscles):	Moderate.	Most cumulative.
$T_{1/2}$	1.5 day	7 days
optimum Plasma concentration:	0.5-2 ng I ml	10-25 ng/ml
Digitalizing dose Initial dose: I.V oral	 0.5-1 mg 0.75-1.5 mg	 …… 0.8-1.2 mg
Maintenance dose	0.25 mg	0.05-0.2mg

Cardiac glycosides (digitalis derivatives)

❖ Mechanism of action:

- Inhibit Na^+/K^+ ATPase (Na+ pump) in cardiac cells → ↑ in intracellular Na^+ → increase in intracellular Ca^{2+} by:

1. ↓ Ca^{2+}/Na^+ exchange.
2. ↑ Release of Ca^{2+} from sarcoplasmic reticulum.
3. ↑ Intracellular Na+ & Ca2+ → ↑ activity of excitable tissues in cardiac & smooth muscle & neurons (CNS) leading to the following effects:
   - Indirect Effects by Vagal (Parasympathetic) stimulation → ↓ S.A.N, ↑Atrial Conductivity &↓ A.V.N.
   - Direct Effects by inhibiting Na^+/K^+ ATPase

1. Positive Inotropic Effect :

- ↑ **Contractility & COP**: (↑ intracellular calcium). → maintains organ perfusion & BP & ↓ baroreflex stimulation of adrenergic (↓ HR) & renin-angiotensin systems (↓ Na+ retention & edema).
- ↓ **H R = negative chronotropic (Bradycardia):** effect by both vagal & direct effects:

	Atrial conductivity	AV conductivity	Ventricular
Direct action	Decrease	Decrease	decrease
Indirect (vagal) action	Increase	Decrease	No effect
Net effect	Variable depending on vagal tone	Profound decrease	decrease

- ↓ AV conduction (negative dromotropic) → A V block, beneficial in supra-ventricular arrhythmias as it protects the ventricles.

- **Excitability**: S.D. → ↑ Excitability, while L.D.→↓.Excitability.

- **Automaticity:** L. D. → ↑ Automaticity specially in Purkinje fibers → Arrhythmias contraindicated in ventricular arrhythmias

2. Renal effect: Digitalis has a diuretic action only in cases of congestive heart failure as it ↑ COP → ↑renal blood flow (RBF) and ↓renin-angiotensin-aldosterone system→ ↑ Na^+ and water excretion.

3. Arterial Blood Pressure:

- Digitalis "normalizes" ABP if it was low as it increases COP.
- ↑ ABP in case of toxicity by V. C. (direct action and by stimulation of VMC).
- Digitalis can be used in patients suffering from hypertensive heart failure

4. CNS effect: They stimulate:

- Vagal (parasympathetic) center → bradycardia in therapeutic doses
- CTZ and visual cortex in toxic doses → vomiting and visual hallucination yellow and green vision (achromatopsia)).

Cardiac glycosides (digitalis derivatives)

❖ Therapeutic uses

1. Treatment of moderate class 3 and severe heart failure class 4 because they increase contractility and diuretic action.
2. Treatment of heart failure associated with atrial fibrillation or flutter because digoxin is the only drug that ↑ contractility and ↓ AV conduction in the same time.
3. Treatment of supraventricular arrhythmia:

- They inhibit AV nodal conduction. This prevents conduction of abnormal impulses from ectopic foci in the atrium to ventricle.

❖ Adverse effects (Toxicity):

- **Due to CNS effects**: Nausia &vomiting, confusion and visual hallucination
- **Due to increase in intracellular calcium**: activation of ectopic foci, ventricular arrhythmias
- **Due to inhibition of SA&AV conduction**: bradycardia (inhibition of SA node), heart block (inhibition of AV node).

Cardiac glycosides (digitalis derivatives)

❖ Treatment of toxicity of cardiac glycosides:

1. Stop digitalis.
2. In case of hypokalemia: stop K^{+}-losing diuretics and give KCl (slowly IV infusion) or orally.
3. In case of hypercalcemia: give Ca2+ chelating agent as sodium edetate IV.
4. To treat A V block use atropine.
5. To treat ventricular arrhythmias With AV block: Phenytoin.
6. To treat ventricular arrhythmias Without AV block: Lidocaine or B-blockers.
7. In case of acute toxicity: Digoxin antibodies (Fab fragments) are given.

❖ Drug interactions:

1) K^{+} -losing diuretics as thiazides and loop diuretics cause hypokalemia and hypomagnesemia which predispose to digitalis toxicity.
2) B-blockers and verapamil antagonize inotropic action of digitalis but augment bradycardia and AV block.
3) Sympathomimetic acting as B1-agonists as adrenaline may lead to ventricular arrhythmia.
4) Ca2+ salts increase the action of digitalis and may lead to toxicity.

Other Positive Inotropic Drugs

A) Phosphodiesterase (PDE) inhibitor:

❑ Bipyridines:

❖ **Preparations:**

1. Amrinone:
2. Milrinone: more potent and less toxic than amrinone.

❖ **Mechanism of action:**

- They inhibit PDE type 3 → ↑ cAMP → ↑ Ca2+ influx in myocardial cells → ↑myocardial contractility →+ inotropic action.
- They have V.D properties.

❖ **Pharmacological actions**:

- Positive inotropic action and V.D. which reduces pre-load and after-load (they are known as "Ino-dilators").
  - ❖ Amrinone: given IV for short-term treatment of acute heart failure. It is highly toxic and may cause, tachycardia, arrhythmia, thrombocytopenia and hepatotoxicity.
  - ❖ Milrinone: more potent and less toxic than amrinone.

Other Positive Inotropic Drugs

B) B_{1-} agonists

❖ Preparations:

1-Dopamine

- Low dose (2-3 µg \minute) causes selective renal vasodilatation and used for treatment of acute renal failure due to D1 stimulation in renal vessels
- Moderate dose of dopamine 5-10 ug/kg/minute has +ve inotropic action. It selectively increases cardiac output and myocardial contractility with no significant effect on heart rate.
- Large doses have α_1 mediated vasoconstriction leading to increase afterload and decrease cardiac output.

❖ Advantages

-Selective renal vasodilatation
-Selective increase in cardiac contractility without Significant effect on heart rate

❖ Disadvantage

-It should be given by intravenous infusion
-Tachycardia &loss of selectivity in large doses
-It needs fine dose adjustment.
-Short action due rapid metabolism.
-Tolerance on prolonged use due to down regulation of B receptors
-Not suitable for long term management of heart failure

Other Positive Inotropic Drugs

2- Dobutamine

- Very short acting. It should be administrated by intravenous infusion.
- Stimulation of B_1 receptors in myocardial muscels (Small dose 2.5-15ug/kg /minute**)** →Increase myocardial contractility &cardiac output
- Stimulation of B_1 receptors in conductive tissue (**Large dose 20ug/kg/minute)** → Increase heart rate (tachycardia) &arrhythmia

❖ Therapeutic uses

1-Acute &severe heart failure
2-Cardiogenic shock

❖ **Side effects:** tachycardia, arrhythmia and tolerance

❖ **Advantages**

-No need to dose adjustment.
-Selective increase in cardiac output
- Less tachycardia in therapeutic dose

❖ **Disadvantage**

-Very short acting.
- It is inactive orally. It should be administrated by intravenous infusion
- Large doses causes arrhythmia and tachycardia.
- Prolonged use leads to tolerance (loss of therapeutic action).

Drugs Therapy of Thrombosis

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Blood disorders

- **Hemostasis:** a complex process → stop of bleeding by vasoconstriction, or by promoting platelet aggregation, blood coagulation.

- **Coagulation disorders** → increased risk of bleeding (hemorrhage) or obstructive clotting (thrombosis).

- **Thrombosis:** a pathological condition resulting from inappropriate activation of the hemostatic mechanisms (platelet aggregation & coagulation) → fibrin formation.

❑ Types of Thrombosis

Arterial thrombosis	Venous thrombosis
Rich in platelets (white thrombus)	Rich in fibrin & RBCs (red thrombus)
Mainly due to atherosclerosis→ interrupt blood flow → ischemia or death of tissue (infarction)	Mainly due to increase clotting factors or slow circulation (pregnancy &sex hormones) →travel to emboli
It causes angina, gangrene peripheral vascular diseases	It causes deep venous thrombosis in lower limb and pulmonary embolism
Treated by anti-platelet drugs & fibrinolytics	Treated by anticoagulant drugs

Blood disorders

❖ Drugs used in treatment of thrombotic disorders

Antiplatelet drugs	Anticoagulant drugs	Thrombolytic drugs
-They act by inhibition of platelet aggregation	They inhibit blood coagulation by inactivating coagulation factors	-They are proteolysis enzymes that dissolve the formed thrombus
-They prevent occurrence of thrombosis -They do not affect already formed thrombus	They prevent propagation and recurrence of thrombosis. They do not affect already formed thrombus.	They dissolve the formed thrombus
They increase traumatic & postoperative hemorrhage	Spontaneous bleeding occurs in large doses	Hemorrhage occur at therapeutic dose.
They do not affect post-thrombotic ischemia	-They do not affect post-thrombotic ischemia	They relieve post – thrombotic ischemia
They increase bleeding time	They increase coagulation time ,partial activated thromboplastin time & prothrombin time and international ratio	They increase all tests for blood clotting

Anticoagulants drugs

Anticoagulants drugs

❖ Classification of anticoagulant drugs

➢ **Indirect inhibit synthesis or activates of the coagulation factors:**

- Parenteral anticoagulants:
  . Indirect thrombin inhibitors: Heparin-LMWHs.
  . Indirect selective inhibitor of factor Xa: fondaparinux.

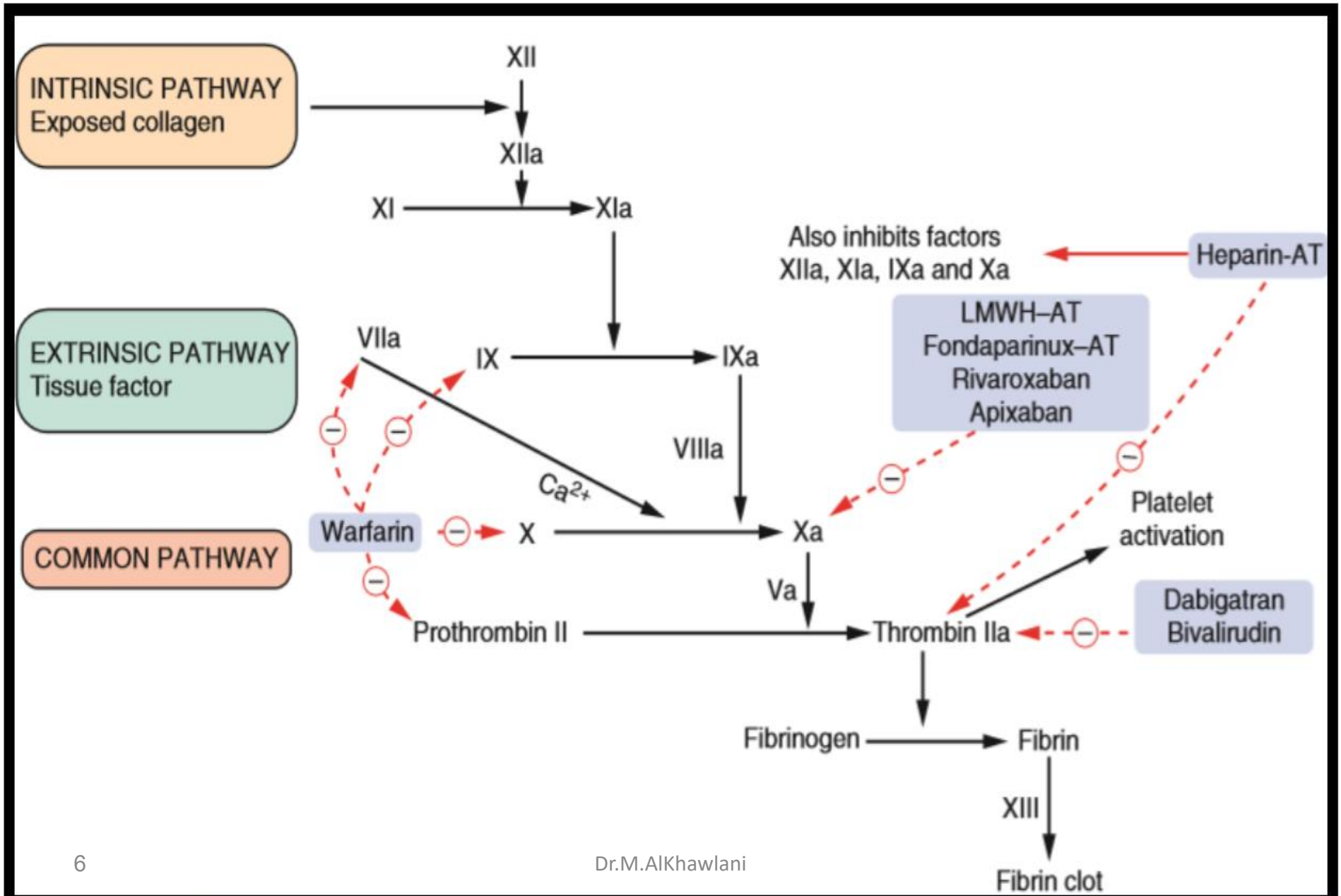
- Oral anticoagulants:
  . Inhibitor of synthesis of clotting factors (II,VII, IX, X), vitamin K antagonists: warfarin).

➢ **Direct inhibitors of coagulation factors:**

- Parenteral anticoagulants: direct thrombin inhibitors: argatroban

- Oral anticoagulants:
  . Direct thrombin inhibitor: Dabigatran.
  . Direct inhibitors of factor Xa: Rivaroxaban.

Anticoagulants drugs



Anticoagulants drugs

A. Indirect thrombin inhibitors:

1- Parenteral anticoagulants: Heparin-LMWHs.

1. Heparin (Unfractionated heparin, UFH)

- Sulfated mucopolysaccharide with high MW.
- Highly acidic with electronegative charge (neutralized by basic molecules eg, **protamine**),
- Present naturally in mast cells and basophils in lung, liver and intestine.
- It is extracted for commercial from porcine or cattle intestinal mucosa.

❖ Pharmacokinetics

- Not absorbed orally. Given **IV** or SC. (not given IM, It produces hematoma) and short duration (4-6h).
- Rapid onset of action I.V(for treatment, 10-20 min).
- Delayed action **SC** (for prophylaxis, 1–2 h) 2 hours preoperative and every 12 hours postoperative for 5-7 days.
- Does not cross BBB or placenta & not secreted in milk (high MW) → used during lactation or pregnancy..
- Rapid metabolism in plasma by heparin neutralizing factor. Rapid excretion in urine.
- The action of heparin is monitored with the activated partial thromboplastin time (aPTT) laboratory test.

❖ Mechanism of action:

- Combines with antithrombin III (natural anticoagulant factor) → forming heparin-antithrombin complex → inactivate factors IIa (Thrombin)- IXa- Xa, XIIa and XIIIa → **anticoagulant effects.**

- **Weak antithrombotic (**inhibition of factor XIII induced clot stabilization)

- **At low concentration**: heparin selectively inhibits the conversion of prothrombin to thrombin → prevents further thrombus formation

- **At high doses**: inhibits platelets function and ↑ vascular permeability → prolongs the bleeding time (BT) → hemorrhagic effects of heparin. (**Weak antiplatelet action**)

- Heparin →↓ the blood lipid level by releasing lipoprotein lipase (LPL).

- Stimulation of other proteases→ osteoporosis , hair loss.
- Stimulation of antiplatelet antibodies → thrombocytopenia
- Depletion of antithrombin → thrombosis
- Inhibition of aldosterone synthesis → Hyperkalemia

2. Low-molecular-weight heparins (LMWHs): molecular weight less than 6000 Da

❖ **Preparation:** Enoxaparin (Clexane)®, Dalteparin and Raviparin

- Produced by chemical depolymerization of unfractionated heparin
- Combines with antithrombin III → inactivate factor Xa, but less effect on factor IIa → **anticoagulant effect**
- Given only SC, the onset of action 4 h

- **Advantages of LMWHs**

  - Equal efficacy to unfractionated heparin.
  - Greater bioavailability from sc sites.
  - longer t½ → 2 – 4 times longer than UFH (given once or twice a day).
  - Less thrombocytopenia & osteoporosis.
  - Less risk of bleeding. (safe not require routine monitoring of anticoagulation activity and dose adjustments in most patients

- **NB:** in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended.

❖ Side effects

- **Bleeding:** hemorrhagic stroke (need dose monitoring)
- **Thrombocytopenia**.
- Hyperkaliemia
- Alopecia (transient) & Osteoporosis after long-term use
- **Hypersensitivity reactions**: urticaria, fever and anaphylaxis.

NB:

- Antidote for heparin is **protamine sulfate**.
- a basic protein that neutralizes the action of acidic heparin .
- It is administrated in a dose of 50 mg intravenous
- Partially antagonizes LMWHs but does not antagonize fondaparinux.

Parenteral poly-sacharride derived indirect non specific antithrombin III activators (heparin & its substitutes)

	High molecualar weight heparins	Low molecular weight heparins	Fondaparinux
Mechanism of action	Binds to both antithrombin III and factor X or II. Increase activity of antithrombin to inhibit factor X=II	Bind to antithrombin III and increase its activity to inhibit factor X (Potent) > II (weak)	Bind to antithrombin III and increase its activity to inhibit factor X only
Efficacy	Rapid, short and very effective	Slow and prolonged and less effective	
Side effect	More frequent hemorrhage , hypolipidemia , thrombocytopenia	Less than heparin	The least . Contra-indicated in patients with renal impairment
Dose adjustment	aPTT should be 3 times more than normal	Not needed due to possibility for hemorrhage	
Administra-tion	**IV bolus** followed by drip in 2nd prevention of already formed thrombus -1ry prevention during hemodialysis or open heart surgery or balloon dilation of blood vessels (coronary & peripheral **-SC**: like LMW heparin but less favorable	Sc: -Long term postoperative to prevent thrombosis in bone surgery -Alternative to oral anticoagulants if contraindicated (pregnancy ,allergy)	As low molecular weight heparin + heparin induced thrombocytopenia
Dose	Heparin sodium or heparin calcium in heart failure to prevent sodium retention	Daltaparin 5000-10000 u twice daily	2.5-5 mg prefilled syringe once daily SC

Dermatan sulfate:-It is used to prevent occurrence of thrombus in cardiac surgery and hemodialysis in a dose of 6mg/kg/day intravenous as an alternative to heparin in cases of heparin allergy.

B. Direct thrombin inhibitors (DTIs):

A. Parenteral DTIs: Hirudin, Bivalirudin, Argatroban

B. **Oral DTIs**:.

- Direct thrombin inhibitor: Dabigatran.
- Direct inhibitors of factor Xa: Rivaroxaban.

- Bind directly to the active site of thrombin without binding to AT III → inhibiting thrombin's downstream effects

❖ Advantages of DTIs:

- Specificity for factor II (thrombin) or factor X
- Do not affect platelet function → not cause heparin induce Thrombocytopenia (HIT) .
- Produce a more predictable anticoagulant effect (because not require AT as a cofactor and do not bind to plasma proteins)
- drugs of choice for the treatment of venous thromboembolism (VTE) in patients with a diagnosis or history of HIT.
- No known antidotes to reverse the effects of the DTIs, but in major bleeding should be given Fresh frozen plasma (FFP).

Anticoagulants drugs

Direct Thrombin inhibitors (DTIs) of enzymatic (serine protease) clotting factor

	Recombinat Hirudin	Bivalirudin ,	Argatroban	Rivaroxiban	Dabigatran
	Parenteral DTIs			Oral DTIs	
Mechanism of action	Non-specific irreversible inhibitor of factor II & antiplatelet	Specific factor II inhibitor	Specific factor IIa inhibitor	Specific competitive factor xa blocker	Specific factor II blocker
GIT absorption	No	No	NO	Rapid , efficient	Poor
Distribution	Limited distribution in extracellular fluid , No passage to BBB or placental barrier. Bivalirudin passes in milk				
Metabolism	No	No	Hepatic	Hepatic	No
Excretion	Renal	Renal	Biliary	Renal excretion	
Action	Immediate action and short duration			Delayed action and long duration	
Therapeutic uses	As HMW or LMW heparin if there is allergy or thrombocytopenia -Cream for skin hematoma			- prophylaxis against thrombosis post-operative in hip or knee surgery, atrial fibrillation ,	
Side effects	hemorrhage ,allergy	Mild hemorrhage , pain at injection site . Dose of argatroban is reduced in hepatic impairment		-Mild hemorrhage Severe hemorrhage - allergy, dose reduction in renal disease	

C. Oral non specific anticoagulants

E.g.: Warfarin

❖ pharmacokinetic

- Well absorbed after oral (small, lipid-soluble)
- Distributed all-over the body and passes B.B.B & Placental barrier.
- Highly bound to plasma proteins (>99%),
- Excessive metabolism by cytochrome P450 enzymes.
- Excreted in urine &billary.
- Onset of action: Delayed after 1-2 days. Duration of action : Long for 5-7 days.

❖ Mechanism of action:

- Inhibit vitamin K epoxide reductase → inhibiting the synthesis of Vit K-dependent coagulant factors (II, VII, IX & X) and endogenous anticoagulant proteins (C & S) → **anticoagulation effect**

- Affect newly formed coagulation factor with no effect on already formed coagulation factors → have slow onset of action (3-5 days after the end of life span)

Anticoagulants drugs

❖ Therapeutic use:

- Prophylactic and treatment of deep venous thrombus (DVT) and PE.
- Prophylactic and treatment of thromboembolism in atrial fibrillation and/or prosthetic heart valves and during orthopedic surgery.

❖ Dosage of Warfarin

- It is administrated as initial dose of 2-5 mg /day for 10 days with parenteral anticoagulant (heparin or fondaparinux) followed by maintenance dose of 10 mg /day for 2-3 month.
- The dose of warfarin are adjusted by prothrombin time (INR ratio) .It should be 2.5 times the normal value

NB : **Antidote**

- vitamin K: administrated in cases of toxicity of warfarin and if a patient on warfarin therapy undergoes surgical operation.

Disadvantages

- Delayed onset
- Narrow therapeutic index
- Requires routine monitoring of coagulation.
- Drug interactions

❖ Side effects

1-Hemorrhage.
2-Paradoxical thrombosis due to inhibition of protein S&C.
4-Teratogenic effect leading to:

- Fetal hemorrhage due to excessive anticoagulant action.
- Bone malformation due to inhibition of vitamin K dependent bone forming enzymes.
- Respiratory distress syndrome due to inhibition of vitamin K dependent pulmonary surfactant.

5-Hemorrhage in sulking infants (concentrated in breast milk).

❖ Contraindications

❑ **liver diseases** due to →↓ hepatic synthesis of coagulation factors → potentates the toxicity of oral anticoagulants.

❑ During pregnancy & lactating.

Anticoagulants drugs

❖ Factors increasing the effects of oral anticoagulants

1) ↓ synthesis of coagulation factors in cases of liver diseases.
2) ↓ vitamin K synthesis by intestinal flora by long term use of broad-spectrum antibiotics.
3) ↓ vitamin K activation by cephalosporins which inhibit vitamin K activating enzyme (vitamin K reductase)
4) ↓ metabolism of oral anticoagulants by enzyme inhibitors e.g. chloramphicol ,cimetidine ,metronidazole .
5) ↑ plasma concentration of anticoagulants by their displacement from plasma protein binding sites by salicylates ,phenylbutazone, NSAID.
6) Inhibition of vitamin K absorption by non-absorbable mineral oils eg paraffin oil.
7) Combination with other inhibitors of coagulation pathway e.g. antiplatelet drugs (salicylates).

❖ Factors decreasing the effects of oral anticoagulants

1) ↓ absorption of oral anticoagulants: by antacids &cholestyramine .
2) ↑ metabolism of oral anticoagulants by HME inducers e.g. barbiturates &rifampicin ,quinolones and grisofulvin.
3) ↑ synthesis of coagulation proteins by estrogen and oral contraceptive pills.
4) High intake of food stuffs containing vitamin K e.g. cabbage.

Anticoagulant therapy

1. **Prophylaxis of deep venous thrombosis / pulmonary embolism** after knee or hip surgery (Heparin, LMWH, fondaparinaux, warfarin, and rivaroxaban.

2. **Treatment of deep venous thrombosis / pulmonary embolism** (heparin followed by warfarin, apixaban, rivaroxaban)

3. Rheumatic valve disease or mechanical heart valves (Warfarin)

4. Chronic coronary or peripheral artery diseases (Rivaroxaban plus aspirin)

5. Arterial thrombosis: coronary, cerebral; Acute coronary syndrome (Heparin)

6.Cardiac & vascular surgery (heparin)- Hemodialysis (heparin).

7. Unstable angina, atrial fibrillation (warfarin).

Protocol for anticoagulation

- IV heparin (initially), for 10 days (rapid action of heparin) followed by IV heparin + oral warfarin for 3-5 days
- warfarin for 2-3 month to prevent recurrence of thrombosis. They may administrated for life in high risk patients (atherosclerosis & pulmonary embolism) or in cases of recurrent thrombosis
- Rivaroxaban is approved as initial oral treatment of deep vein thrombosis (DVT).
- If a patient on warfarin undergoes surgical operation ,Do not stop warfarin but give vitamin K, 3 days before operation.

Drugs Therapy of Thrombosis

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Thrombolytic drugs

Thrombolytic drugs

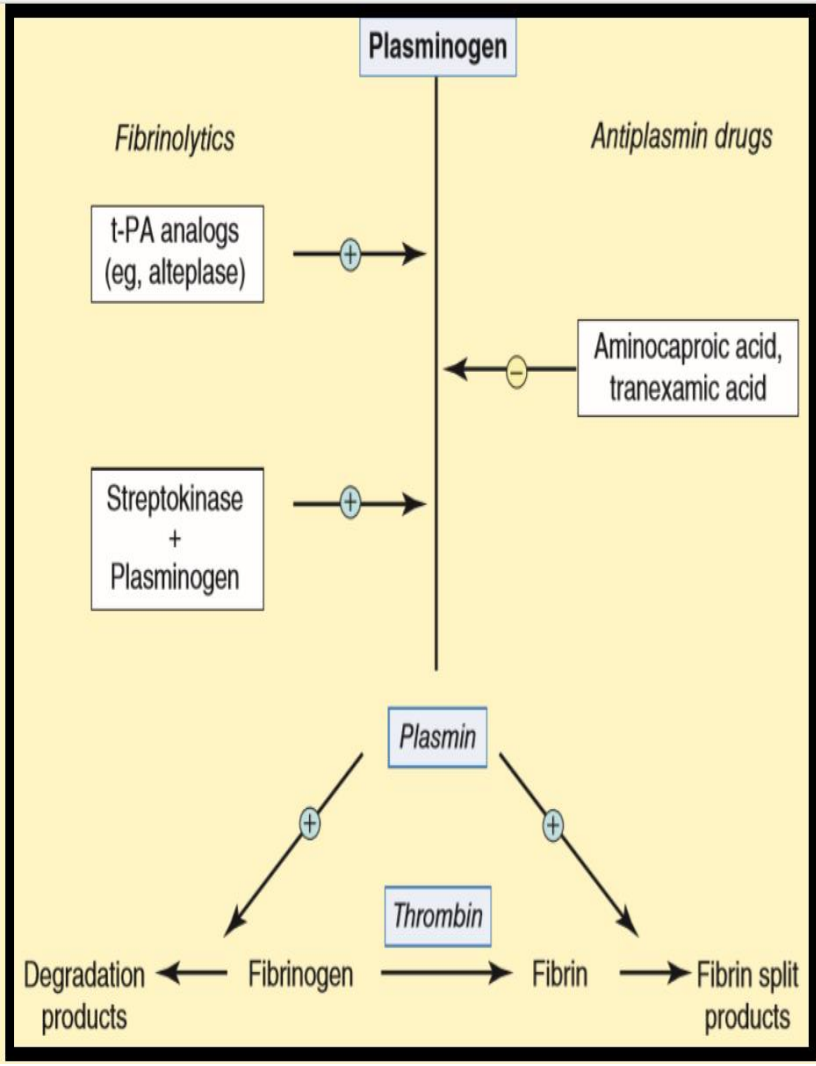
2. Thrombolytic (fibrinolytic)

- Drugs that cause lysis of thrombus. Given IV route

❖ Mechanism of action

- Fibrinolytics are plasminogen activators. → activate plasminogen to plasmin → degradation of both thrombotic fibrin (dissolve clot), circulating fibrinogen and factors V & VIII (bleeding problems)

- The ideal fibrinolytic is fibrin-specific without activating free plasminogen in plasma → its effect is localized to clot → ↓ risk of bleeding.



❖ Classification of Fibrinolytics

➢ **Fibrin-Nonspecific : Streptokinase, urokinase**

➢ **Fibrin-specific: Tissue Plasminogen Activators analgs, alteplase, Reteplase, Tenecteplase,)**

Thrombolytic drugs

1. Fibrin-Nonspecific : Streptokinase, urokinase

- Non fibrin-selective: activate both circulating & clot (fibrin)-bound plasminogen → degradation of thrombi, physiological clots and circulating clotting factors:

- **Streptokinase**:
  - Acts indirectly by bind to plasminogen → complex → activates free plasminogen to plasmin
  - derived from β –hemolytic streptococci →Antigenic & allergic reaction and drug resistance

- **urokinase**: directly activates plasminogen to plasmin
  - Derived from human kidney
  - It is as hemorrhagic and less antigenic than streptokinase

❖ **Disadvantages**
- bleeding risk
- Antigenic (**Streptokinase**).
- Given as intravenous.

Thrombolytic drugs

2. Fibrin-specific: alteplase, Reteplase, Tenecteplase

- fibrin-selective: Breakdown fibrin clots with no effect on circulating clotting factors
- Alteplase (human tPA): recombinant DNA technology.& Tenecteplase: mutant of tPA.

- **Advantages**

  - ↓ bleeding risk (fibrin-selective).
  - Nonantigenic.
  - Tenecteplase & Reteplase: have longer plasma half-lives than alteplase.

❖ Indications of Fibrinolytics

1. Prevent post thrombotic ischemia if administrated early after occlusion of blood vessels before the occurrence of post ischemic cell death (infarction)
2. Acute myocardial infarction (most effective if given early with in 12 hours).
3. Cerebral thrombosis (with in 3-6 hours)
4. Occlusion of peripheral blood vessels in upper and lower limbs (with in 24 hours)
5. Pulmonary embolism. Deep venous thrombosis.

Thrombolytic drugs

❖ Adverse effects:

- Bleeding (more with fibrin-non specific agents) → treated by stopping infusion, fresh blood & antifibrinolytics).
- Antigenicity (fever, allergy & hypotension) with streptokinase→ start therapy with a large loading dose to neutralize antibodies).
- Recurrence of thrombosis.

❖ Contraindications:

- In pregnancy
- patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.

Antiplatelet drugs

3. Antiplatelet drugs

- Drugs that inhibit platelet aggregation

❑ Classification of antiplatelets according to mechanism of Action

1. Inhibition of Thromboxane (TXA2) synthesis: Low-dose aspirin.
2. Inhibition of ADP-induced platelet aggregation (clopidogrel, prasugrel, ticlopidine),
3. Inhibition of Phosphodiesterase (PDE): Dipyridamole, Cilostazol
4. Blockade of glycoprotein IIb/IIIa (GP IIb/IIIa) receptors on platelets (abciximab, tirofiban, and eptifibatide).

A. **TXA2 synthesis inhibitor:** Acetyl salicylic acid (Aspirin): oral once/day

- Low-dose aspirin (75–325 mg/d) → irreversible inhibition of COX-1 enzyme in platelets by acetylation→ inhibition of synthesis of TXA_2 in platelets→↓ platelet aggregation (the antiplatelet effect lasts for the life-time of the platelets, i.e. 7–10 days).

- Large dose (anti-inflammatory dose 300 mg TID) has no antiplatelet action because it inhibits synthesis of both PGI2 and TXA2.

- Aspirin is the main antiplatelet drug used. Clopidogrel or dipyridamole may be combined to it or given to patients intolerant to it.

Antiplatelet drugs

B. ADP-receptor inhibitors: Ticlopidine , clopidogrel (Plavix)®, prasugrel & ticagrelor (oral)

- They irreversibly inhibit the binding of ADP to its receptors on platelets → ↓ activation of the GP IIb/IIIa receptors on platelets to bind to fibrinogen → ↓ platelet aggregation.
- They produce synergistic effect when combined with aspirin or GP-IIb/IIIa receptor antagonists

C. GP IIb/IIIa receptor antagonists: Abciximab, eptifibatide and tirofiban

- They are monoclonal antibody that block GP IIb/IIIa receptors for fibrinogen on platelet surface → inhibiting the final step in the process of platelet aggregation.
- These drugs are administered parenterally.

D. Phosphodiesterase 3 inhibitor: Dipyridamole & Cilostazol

- Inhibits PDE →↑ the concentration of cAMP levels → inhibits platelet aggregation.
- Vasodilator & antiplatelet.
- Dipyridamole is a weak antiplatelet → combined with warfarin or aspirin.
- Dipyridamole: preferred to aspirin for combination with warfarin (less bleeding).

Antiplatelet drugs

❖ **Therapeutic uses of antiplatelet drugs** (mainly in arterial thrombosis)

1. In high risk patients (atherosclerotic & hyperlipedemic & hypertensive &old age) myocardial infarction (MI) (aspirin)
2. Acute coronary syndrome (aspirin + clopidogrel or abciximab).
3. Coronary bypasses grafting, angioplasty & stent insertion (aspirin plus Clopidogrel or abciximab).
4. Prosthetic heart valves: ↓ thrombo-embolism (dipyridamole plus warfarin).
5. Transient ischemic attacks- thrombotic stroke (dipyridamole plus aspirin).
6. Hemodialysis- cardiopulmonary bypass- pulmonary hypertension (epoprostenol).
7. Intermittent claudication (cilostazol).

.

❖ **Side effects of antiplatelet drugs:**

1.Aspirin: gastric irritation and bleeding time, allergy, Reye's syndrome, Hyperuricemia

2. Ticlopidine: GIT irritation – neutropenia

3. Clopidogrel; preferred to ticlopidine; less risk of neutropenia)
- Bleeding-rash- Gastric irrigation,, diarrhea.
- Clopidogrel is a prodrug → avoid with omeprazole as it inhibits its activation in liver.

Antiplatelet drugs

4. Prasugrel: ↑ Risk of bleeding (CI in patients with history of transient ischemic attack (TIA) or stroke because bleeding risk

5. Ticagrelor: bleeding- shortness of breath

6. Dipyridamole: headache and orthostatic hypotension (esp if administered IV).
   - **CI** in unstable angina because of its vasodilating properties → worsen ischemia (coronary steal phenomenon).

7. Epoprostenol: Flushing, headache, hypotension.

8. Abciximab : bleeding, thrombocytopenia, arrhythmia.

9. Cilostazol (oral):
   - Headache, dizziness- GIT upset: nausea, dyspepsia, diarrhea
   - Tachycardia, palpitations, peripheral edema.

NB: Aspirin should not be added to anticoagulant therapy except in specific conditions e.g. recent acute coronary syndrome or stent placement.

Hemostatic drugs
Drugs used in bleeding

Drugs used in bleeding

1. Vitamin K

- Vitamins K1 (Phytonadione; is found in food), important for the formation of clotting factors: Prothrombin, Factor VII, Factor IX and Factor X
- Vitamins K2 (Menaquinone; is found in human tissues and is synthesized by intestinal bacteria)
- Deficiency of vitamin K → hemorrhage.
- Given by the IV, SC, IM or oral route
- The response to vit K requiring 24 h (time to synthesize new coagulant factors)

- **Used**

  - Hemorrhagic (hypoprothrombinemia) diseases in newborn.
  - As antidote for warfarin toxicity, in patients receiving oral antibiotics.
  - Vitamin K deficiency (in obstructive jaundice or malabsorption syndrome)

❑ **Side effects:** IV injection may cause flushing, sweating, dyspnea, hypotension.

Drugs used in bleeding

2. Aminocaproic acid & Tranexamic acid

- Block the conversion of plasminogen to plasmin → inhibit fibrinolytic activity → inhibit bleeding due to excessive fibrinolysis.
- Both agents are synthetic, orally active, excreted in the urine.
- Tranexamic acid is 10 times more potent than aminocaproic acid.

- **Clinical uses**;
  - adjunctive therapy in hemophilia,
  - Therapy for bleeding from fibrinolytic therapy, following tooth extraction, tonsillectomy, prostatectomy. .
  - Postsurgical gastrointestinal bleeding and post prostatectomy bleeding and bladder hemorrhage
- **Adverse effects**; iv thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea

3. Etamsylate: (Dicynone)®

- Activate endothelium – platelet interaction.
- ↑ Platelet adhesiveness and restoring capillary resistance.
- Given orally and parenterally.

Drugs used in bleeding

4. Protamine sulfate

- Antagonizes the anticoagulant effects of heparin. .
- The +ve charged protamine interacts with the -ve charged heparin, → a stable complex without anticoagulant activity.

- **Adverse effects:** hypersensitivity, dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

Drugs Used in Hyperlipidemia

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Hyperlipidemia

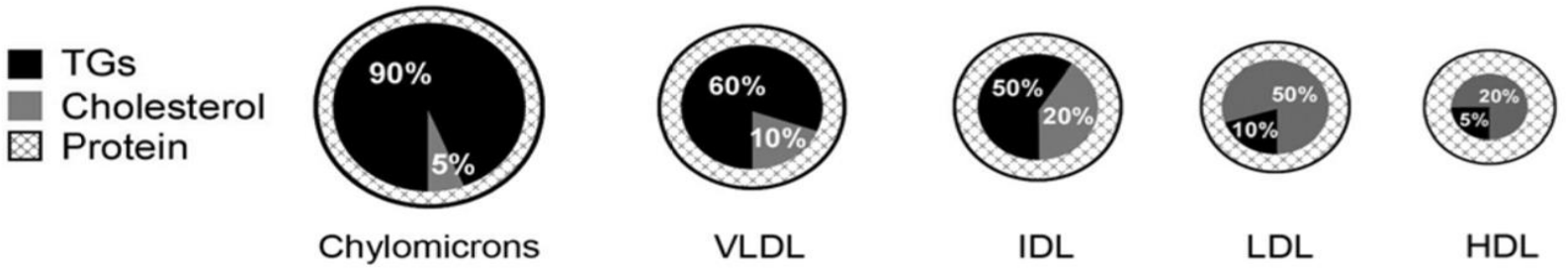
❖ **Hyperlipidemia** is the increasing the serum concentrations of cholesterol or triglycerides or both to levels associated with a risk of ischemic heart diseases (IHD).

- Cholesterol and TGs are insoluble in blood → therefore carried in combination with specific proteins (apoproteins) → forming lipoproteins (water soluble).

- **Lipoproteins consists of** :
  - Inner hydrophobic lipid core (triglycerides & cholesterol ester) .
  - Outer coat consisted of free cholesterol apolipoproteins and phospholipids.

❖ Types of lipoproteins

1. Chylomicrons: Triglycerides (TG) > cholesterol (Ch).
2. Very low density lipoproteins (VLDL): TG > Ch.
3. Low density lipoproteins (LDL), harmful (atherogenic) lipids: Ch > TG.
4. High density lipoproteins(HDL), useful (non-atherogenic) lipoproteins : Ch > TG



NB: Atherogenic lipids are LDL, oxidized LDL, and chylomicron ruminants.

❖ Etiology & classification of Hyperlipidemias:

1. **Primary:** (congenital hyperlipidemia): hereditary.

Class	Increased lipoprotein	Synonym
Type I	↑ chylomicrons	Familial chylomicronemia
Type IIa	↑ LDL	Familial hypercholesterolemia
IIb	↑ LDL and VLDL	Familial combined hyperlipidemia
Type III	↑ IDL	Familial dysbetalipoproteinemia
Type IV	↑ VLDL	Familial hypertriglyceridemia
Type V	↑ VLDL and chylomicrons	Familial mixed hyperlipedemia

2. **Secondary:** due to other diseases

- **Hypertriglyceridemia**: Diabetes mellitus, chronic nephrosis, obesity
- **Hypercholesterolemia**: Hypothyroidism, nephrotic syndrome.
- **Drugs**: B blockers, diuretics, alcohol, Estrogen &contraceptive pills &androgen &anabolic steroids

Hyperlipidemia

Complications of hyperlipidemia

- **High plasma LDL** → ↑ plasma cholesterol which leads to:

❖ Atherosclerosis → ↑ susceptibility of ischemic heart diseases and cerebral stroke.

❖ Cholesterol containing skin lesions (xanthoma).

-**High plasma VLDL** → ↑ plasma triglycerides which leads to:

❖ Increased susceptibility to ischemic heart diseases.

❖ Obesity

Non-pharmacological therapy:

- Avoid saturated fatty acids (animal fat) containing cholesterol.
- ↑ Consumption of unsaturated fatty acids (plant fats) and dietary fibers.
- Stop smoking & alcohol.
- Weight reduction and regular exercise.

Drug therapy in hyperlipidemia

1 HMG-CoA Reductase Inhibitors (Statins)

Simvastatin, Rosuvastatin , Atorvastatin, Pravastatin, Fluvastatin, Lovastatin Pitavastatin

❖ Pharmacokinetics

- Absorbed orally. All statins are taken orally at bedtime because of diurnal, increase cholesterol synthesis in the evening, except atorvastatin, rosuvastatin and pitavastatin are taken at any time because of their long half-life atorvastatin (14 hours), pitavastatin (12 hours), and rosuvastatin (19 hours).
- Metabolized in the liver by the cyto P450, Excretion in bile, faeces and urine

❖ Mechanism of action:

- ↓ HMG-CoA reductase enzyme → ↓ cholesterol synthesis in liver → depletion of intracellular cholesterol → ↑ number of LDL receptors on liver cells → ↓ LDL in plasma. .
- ↑ HDL in some patients & ↓TGs & VLDL (to some extent)
- Cardioprotective: vasodilators- ↓ platelet thrombus formation → ↓atherosclerosis (stabilize plaque), and anti-inflammatory activity

Drug therapy in hyperlipidemia

❖ Therapeutic uses:

- Hypercholesterolemia, **(Type IIa,** reducing levels of LDL **)**).
- With other drugs in Combined hyperlipidemia (**Type IIb,** ↑ cholesterol and TGs).
- Used as a prophylaxis in MI and stroke.

- Potency as LDL cholesterol–lowering statins: Pitavastatin, rosuvastatin, and atorvastatin > simvastatin, pravastatin, > lovastatin and Fluvastatin.

❖ Adverse effects:

- Hepatitis (↑Mild serum aminotransferases) → are common but are not often associated with hepatic damage.

- Myopathy (↑ creatin kinase) in patients with renal impairment especially when combined with fibrates or nicotinic acid.

- Drugs that inhibit cyto P450 activity increase the risk of hepatotoxicity and myopathy.

❖ **Contraindicated** in pregnancy and lactation (cholesterol is important for normal development, and it is possible that statins could cause serious problems).

2-Bile acid-binding resins (Ion exchange resin)

❖ Preparations

-Cholestyramine, Colestipol.

- Colesevelam: has fewer side effects

❖ Pharmacokinetics:

- Bile acid sequestrants are insoluble in water and have large molecular weights.
- After oral administration, they are neither absorbed nor metabolically altered by the intestine.
- They are totally excreted in feces

❖ Mechanism of action:

- Anion exchange resins bind with bile acids in the small intestine → preventing the bile acids from returning to the liver → ↓ the bile acid concentration → ↑ conversion of cholesterol to bile acids → ↓ the intracellular cholesterol concentration.

- ↑ Hepatic uptake of cholesterol-containing LDL particles → ↓ LDL concentration.

Drug therapy in hyperlipidemia

❖ Therapeutic uses:

1. Hypercholesterolemia (in addition to statins when response to statins is inadequate or in cases where statins are contraindicated), LDL cholesterol– lowering effects **(Type IIa)**
2. Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis

❖ Adverse effects:

- GI disturbances: constipation, nausea, and steatorrhea.
  - Colesevelam has fewer GI side effects.

- ↓ Absorption of digitalis, warfarin and tetracycline (binding).
  - Colesevelam does not bind digoxin, warfarin, or reductase inhibitors.

- ↓ Absorption of fat soluble vitamins (A, D, E, and K)

- **Contraindicated** in patients with significant hypertriglyceridemia (≥400 mg/dL) (Raise triglyceride levels and in pregnancy.

3- Fabric acid derivatives (Fibrates), Activators of Lipoprotein Lipase

- lower serum triglycerides (VLDL) & in some patients, LDL and increase HDL levels.

As: Fenofibrate & Gemfibrozil

❖ Mechanism of action

- Agonists for Peroxisome Proliferator–Activated Receptors (PPARs) →↑ expression & activity of plasma of lipoprotein lipase → hydrolysis of VLDL and chylomicrons →↓serum TGs levels.
- Also increase uptake of LDL by liver & ↑ level of HDL
- Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.

❖ Therapeutic uses:

- Hypertriglyceridemia **(Type III, IV)** - mixed hyperlipidemia **(Type V)**
- Combined hyperlipidemia **(Type IIb)** if statins are contraindicated

- Given orally

❖ Adverse effects:

1. GIT disturbances: nausea, vomiting.
2. Formation of gallstones (↑ biliary cholesterol excretion)
3. Myopathy → ↑ Creatine kinase. when combined with statins. (gemfibrozil + statins)
4. Hepatotoxic → ↑Transaminases

- Both fibrates Compete with the warfarin and sulfonylureas for binding sites on plasma proteins. (monitoring INR).

❖ Contraindication

- In liver & kidney diseases or gallbladder disease.
- Not combined with Statin → Severe Liver & Muscle damage. (**CI** of use of gemfibrozil with simvastatin).

- Pregnancy (category C).

Drug therapy in hyperlipidemia

4- Niacin (nicotinic acid) (vitamin B3) As: Niacin

- ↓ both TGs (VLDL) & cholesterol (LDL) levels and ↑ HDL levels.

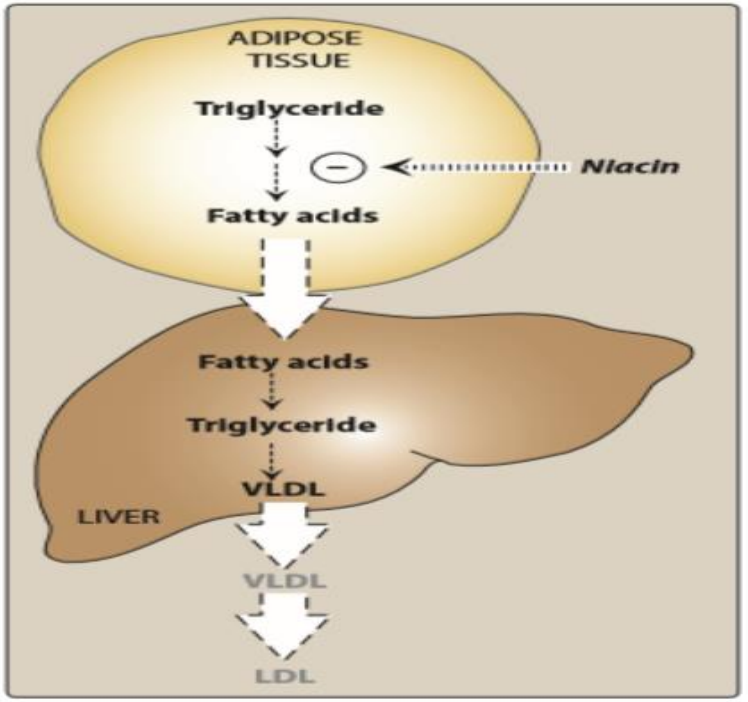


Figure 23.8
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma. VLDL= very-low-density lipoprotein; LDL = low-density lipoprotein.

❖ Mechanism of action:

- ↓ lipolysis of triacylglycerol in adipose tissue to free fatty acids → ↓ triacylglycerol synthesis in liver → ↓ VLDL & LDL.
- ↑ HDL cholesterol level.
- ↑ Secretion of tissue plasminogen activator and ↓ level of plasma fibrinogen

❖ Therapeutic Uses

- Combined with other drugs to treat all types of hyperlipidemia (hypercholesterolemia and hypertriglyceridemia).
- Niacin is administered orally 100 mg bid or tid with meals.

❖ **Adverse effects:**

- Cutaneous vasodilation → flushing and itching (↑ PGs). Prevented by aspirin
- Nausea, abdominal pain and gastric distress (avoided in peptic ulcer). .
- Hyperuricemia. (↓ uric acid excretion)
- Hyperglycemia and hepatotoxicity.

❖ **Contraindication:** in hepatic disease, gout, Pregnancy (category C) & lactation

4- Cholesterol absorption inhibitors:

As: Ezetimibe: 5-20 mg/d

- Inhibits selectively absorption of dietary and biliary cholesterol in the small intestine → ↓ the delivery of intestinal cholesterol to the liver → ↓ hepatic cholesterol stores and ↑ clearance of cholesterol from the blood.

- Used in hypercholesterolemia together with statins & diet regulation.
- Used with caution in hepatic impairment

NB: There are no significant interactions with warfarin or digoxin.

Drug therapy in hyperlipidemia

❖ Combination drug therapy

- ↑ VLDL during treatment of hypercholesterolemia with resins.
- Severe hypertriglyceridemia or hypercholesterolemia.
- If no improvement within 6 weeks with a single drug, dose should be ↑.
- If no improvement after 3 months, change to combination therapy:

1- Cholestyramine + Statin → ↓↓Cholesterol. (**Hypercholesterolemia, Type IIA**)

2- Cholestyramine + Nicotinic acid → ↓↓ TG & cholesterol (**combined hyperlipidemia**)

2- Fibrate + Nicotinic acid → ↓↓ TG & cholesterol (**Hypertriglyceridemia, Type III, IV, V**)

3- Fibrate + Cholestyramine → ↓↓ BOTH TG & cholesterol. (**combined hyperlipidemia**)

4-Fibrate (except fenofibrate) + Statin → Severe Liver & Muscle damage.

5- Ezetimibe + statins (synergistic effects) → ↓↓Cholesterol. (**Hypercholesterolemia**)

Drug therapy in hyperlipidemia

Drug therapy of hypertriglyceridemia

- hypertriglyceridemia with risk of atherosclerosis or coronary heart diseases or severe hyperglyceridemia:

-**Initial therapy**: Fabric acid derivatives or statins.
-Fabric acid derivatives + nicotinic acid.
-Fabric acid derivatives + Nicotinic acid +Fish oil.

Drug therapy of hypercholesterolemia

- hypercholesterolemia with risk factors for coronary heart diseases or coronary bypass operations or severe hypercholesterolemia:

-**Initial therapy:** Bile acid-binding resins or Statin.
-Resin + nicotinic acid.
-Statin +nicotinic acid

- **Treatment of mixed hypertriglyceridemia**

- Hypertriglyceridemia should be treated first because the use of LDL lowering agents alone may exacerbate hypertriglyceridemia

- Then resin + fabric acid derivatives.
- Statin + fabric acid derivatives.

NB: gemfibrozil +fabric acid derivatives potentiate the myopathic effect of each other leading to severe myopathy.

Peptic ulcer

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Peptic Ulcer

- **Peptic ulcer** is a damage of the mucosal lining of the stomach (**gastric ulcer**) or the duodenum (**duodenal ulcer**) due to imbalance between aggressive factors and protective factors

- **Gastroesophageal Reflux Disease (GERD):** ulceration of esophageal mucosa by regurgitation of gastric HCL to esophagus through incompetent lower esophageal sphincter) - Reflux symptoms (e.g. heart burn).

- **Gastritis:** Diffuse inflammation of gastric or duodenal mucosa

Aggressive factors:	Protective factors:
1. **Gastric HCl.** 2. **Pepsin (protein digestive enzyme)** 3. **Infection with Helicobacter Pylori. Bacteria.**	1. Mucous 2. Bicarbonate 3. Prostaglandins E_2

Peptic ulcer

❖ Causes of peptic ulcer:

- ↑ Secretion of HCl.
- Helicobacter pylori. (70-90 %)
- ↓ Mucous and bicarbonate secretion.
- Drugs as NSAIDs, Corticosteroids (inhibit the PG and mucous layer formation). and iron.
- High stress.
- Some diseases as Zollinger-Ellison syndrome.
- Smoking, alcohol, Spicy foods, tea, coffee.

❖ Clinical picture:

1- Epigastric pain and tenderness.
2- Nausea and vomiting.
3- Complications: bleeding, perforation and peritonitis, pyloric obstruction.

Peptic ulcer

❖ **Drugs used include:**

1. ↑ **HCI secretion treated by:**
   - **Antacids (**Neutralize HCl)
   - **Anti-secretory drugs:**
     - **Proton pump inhibitors (**most effective),
     - **H2 receptor blocker**: (Moderate efficacy and safety).
     - **Anticholinergic, Gastrin antagonists drugs (**weak effect).
     - **PGE2 analogue (**Misoprostol)

2. Inadequate mucosal defense against HCI: treated by:
- **Mucosal Protectives (cytoprotective agent)**: misoprostol, Sucralfate, Carbenoxolone Colloidal bismuth.

3. Infection with H. pylori: treated by
- anti *H. Pylori* therapy (antibiotics plus antisecretory drugs).

1- Antacids

- Antacids are weak bases that reduce gastric acidity by neutralizing HCL.

❖ Preparations:

1. **Systemic antacids**: Sodium bicarbonate, calcium carbonate
2. **Local antacids:** Magnesium tricilicate, magnesium hydroxide, aluminum hydroxide

❖ Pharmacological Actions:

1. Neutralization of HCI → ↓ Relief of Pain.
2. Elevation of pH → ↓ Activity of Pepsin.

❖ Therapeutic Uses (taken 1 and 3 hours after meals & at bed time)

1. As symptomatic relief of hyperacidity → Rapid relief (Supplement other drugs during initiation of treatment).

2- GERD & Heart burn and Gastritis

❖ Drug interactions: .

a. Ca^{+2}, Mg^{+2} & Al^{+3} → ↓absorption of Tetracyclines.
b. Mg^{+2} & Al^{+3} → ↓ Absorption of Warfarin, Ranitidine, Digoxin, Theophylline, Iron, Quinolones (Antibiotic) & Ketoconazole (Antifungal).
c) Antacids → ↓ effect of Sucralfate as it needs acid medium to act

A. Systemic antacids: (Soluble and absorbable → systemic alkalosis).

1. Sodium bicarbonate (NaHCO3):

- Quick onset and short duration of action..
- **Disadvantages:**

  - Causes systemic alkalosis→ on long term use.
  - alkalization of urine → Precipitate phosphate stones & ↓ Excretion of weak basic drugs as ephedrine.
  - ↑ Na concentration dangerous in HF, hypertension or renal disease.
  - CO2 release→ Distention, Discomfort, Rupture & Rebound Hyperacidity

- Sodium bicarbonate is also used to:

  - Alkalinize urine → treatment the weak acidic drugs toxicity as salicylates.
  - In gout (↑ excretion of uric acid) and to treat acidosis

2. Calcium carbonate (CaCO3)

- Partially absorbed antacid, less soluble (50% , absorb) and reacts more slowly than NaHCO3 with HCl to form calcium chloride +CO_2

- **Disadvantages:** CO2 Release, Alkalosis, Constipation. Hypercalcemia, and hypercalciuria, Rebound Hyperacidity

B. Local antacids: (Insoluble and not absorbed → no systemic alkalosis.)

1. Magnesium hydroxide: Mg (OH)2

- Has delayed onset of action and long duration.
- Not absorbed, NO systemic alkalosis
- No CO2 release. no gastric distension, no rebound Hyperacidity
- They slowly reacts with gastric HCL forming magnesium salts → causes **diarrhea** due to local intestinal irritation

2. Aluminum hydroxide: Al (OH)3

- Has delayed onset of action, long duration and Very effective:
- NO CO2 release. NO systemic alkalosis.
- Causes constipation. (astringent) and phosphate depletion (induce osteomalacia, hypophosphatemia)

NB: Aluminum salts cause constipation and magnesium salts cause diarrhoea; so combination of these two can counteract the adverse effects of each other.

Maalox = $Mg(OH)_2 + Al(OH)_3$ → synergism with less side effects.

3. Magnesium tricilicate forms protective layer over gastric mucosa (cytoprotective) delayed onset of action, Long duration, No C02 release, No alkalosis, Very effective and causes **diarrhea**

2. Anti-secretory dugs

- They reduce HCI secretion from the parietal cell of the stomach, and are used for healing of the ulcer.

1. Proton Pump Inhibitors (PPIs):

❖ **Preparation:** Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole, Esomeprazol

- Absorbed orally (enteric-coated tablets), Omeprazole, lansoprazole and pantoprazole may be given IV.
- Metabolized in the liver by CYP 450 and metabolites are excreted in urine,
- Oral once daily before breakfast

- Slowest onset because they need activation by gastric HCL (They are prodrugs)
- long duration (2 days after drug stoppage).The time required for synthesis of new pump

❖ **Mechanism of action**: Most effective acid suppressants.

- They are prodrugs and are activated at acidic environment of parietal cells of the stomach → Irreversible inhibitor of H+/K+ ATPase enzyme. Their effect is prolonged until synthesis of new H+/K+ ATPase enzyme.
- Very effective, Inhibit 98% of both basal and meal stimulated gastric HCL

❖ Therapeutic uses:

1. 1st choice in **Peptic ulcer**:,- Given for 4 weeks in duodenal ulcer, and for 8 weeks in gastric ulcer.
   - In acute bleeding ulcers, intravenous PPIs are preferred
   - H. pylori-associated ulcers: Combination therapy most effective regimen for these ulcers.
   - Stress ulcers: Prophylactic use of oral omeprazole /intravenous PPIs
   - NSAID-induced ulcers: more effective than H2-blockers in the prevention and treatment of NSAID-induced ulcers.

2. 1st choice in **GERD & Zollinger-illison syndrome**.

❖ Adverse effects:

1. GIT disturbances: nausea, abdominal pains, diarrhea.
2. Due to decrease GIT absorption of HCL dependent iron (anemia), calcium (osteoporosis).
3. Due to inhibition of secretion of intrinsic factor for vitamin B12 absorption: megaloblastic anemia.
4. Due to increase gastric pH: Inhibition of absorption of acidic drugs (warfarin, fluoroquinolones

❖ Drug interactions:

- Omeprazole is a HME inhibitor (inhibit CYP 450) and decrease clearance of warfarin, theophylline, phenytoin, and diazepam.

2. H2- receptor antagonists:

❑ Preparation:

- **Cimetidine** (not widely used due to dangerous side effects)
- **Ranitidine** (Zantac)® & **Nizatidine** (150mg bid or 300mg at bedtime)
- **Famotidine** (most potent, 20mg bid or 40mg at bedtime).

- Well Absorbed orally & Parentally, Distributed all over the body. Passes BBB & Placental barrier, metabolized in liver, Excreted Unchanged in Urine & Milk.
- The onset of action 1-2 hours & Short duration 6-10 hours

❑ Mechanism of action:

- Reversible competitive antagonists of H2 receptors → decrease secretion of gastric acids (HCl and pepsin)
- Potent inhibition of nocturnal or fasting but less inhibition of daytime (meal-stimulated acid secretion). also reduce acid secretion stimulated by ACh, gastrin.

- Cimetidine has anti-androgenic effects (block of androgen receptors) → Gynecomastia and infertility and loss of sexual desire in males, & CNS side effects and enzyme inhibiting

1. Ranitidine and nizatidine have the same potency and are more potent and have longer duration than cimetidine.
2. Ranitidine: Anti- H pylori effect (most efficient), 50% oral bioavailability (1st - pass effect), 50% metabolized in liver (**CI** in hepatic dysfunction).
3. Nizatidine is not metabolized and has 100% oral bioavailability. Used in liver dysfunction
4. Famotidine is more potent than ranitidine and nizatidine. Cytoprotective effect. Excreted mainly by kidney (preferred in liver dysfunction).

5. Ranitidine, famotidine, and nizatidine have the following advantages over cimetidine:

- Stronger.
- Longer duration.
- No HME inhibition and accordingly no drug interactions.
- No passage across BBB and accordingly no CNS disturbances.
- No antiandrogenic effect and no hyperprolactinemia, and accordingly no sexual disturbances in males or females.

❑ Therapeutic uses:

- Gastric ulcers & duodenal ulcer (reduce nocturnal acid secretion, accelerate healing, and prevent recurrences)
- GERD, Heart burn (PPI are preferred).
- Zollinger- Ellison Syndrome. (PPI are preferred).

❑ Side effects with cimetidine:

- Anti-androgenic action→ impotence, gynecomastia in men and galactorrhea in women.
- CNS disturbances → confusion, sedation, hallucination
- Hepatic microsomal enzyme inhibitor→ ↑ action of other concomitant drugs.
- **Side effects of other H2-blockers**: diarrhea, headache and fatigue.

Peptic ulcer

Cimetidine	Ranitidine	Famotidine	Nisatidine
-Weak H2 blocker 6-8h	-Potent H2 blocker, 12 h	Most Potent, Long acting, 24 h H2 blocker	Rapidly acting H2 blocker
Potent microsomal enzyme inhibitor	Weak microsomal enzyme inhibitor	No effect on microsomal enzymes	No effect on microsomal enzymes
Potent inhibitor to male sex hormones	No effect on male sex hormones	No effect on microsomal enzymes	No effect on microsomal enzymes
CNS side effects	Less CNS side effects	Less CNS side effects	Less CNS side effects
-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis -Treatment of hisutism	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis

❖ Advantages of PPIs over H2 antagonists:

- Higher efficacy → better symptomatic relief & higher response rates.
- More prolonged effect (24hs→ given in single daily dose; versus twice Daily dosing with H2 antagonists).
- More effective in anti H.pylori regimen.

3. Anticholinergic drugs:

- Specific M1 blockers (pirenzepine & telenzepine) are rarely used due to weak effect.
- Not widely used, substituted by H2-blockers.
- They inhibit only stimulated HCL secretion. It is only effective in nicotine induced peptic ulcer.
- They are contraindicated in reflux esophagitis because they relax esophageal sphincter.

3. Mucosal protective agents (cytoprotective agent):

1. Prostaglandins:

As: Misoprostol.

- It is a prostaglandin E1 analogue, cytoprotective agent, With oxytocic properties.
- ↓ Secretion of HCl (**anti-secretory agent**) and ↑ Mucous and bicarbonate production (**mucosal protective agent**) → promote ulcer healing. -
- . Absorbed from GIT, Rapid onset (30 minutes), short duration (3 hours), potent, Given orally 100-200 µg qid
- it is used for NSAID-induced gastric ulcer (healing effect) if PPIs fail
- Also used as prophylaxis of ulcers caused by glucocorticoids and NSAIDs.
- It causes abdominal cramps and diarrhea.

It is contraindicated in pregnancy because it is a powerful oxytocic and may lead to abortion

2. Sucralfate (Aluminum sucrose sulphate): Composed of Sulfated Sucrose+ AI (OH)

❖ Mechanism of action:

- Activated in presence of acid Forms a complex gel with mucus → Adheres to mucous membrane & Ulcer floor →Physical barrier → prevent the degradation of mucous by HCl and pepsin → stimulate healing and prevent recurrence.
- Stimulates prostaglandin release → Increases mucous and bicarbonate production.
- Require acidic PH for activation, so it's not administrated simultaneously with H2-blockers, antacids or proton pump inhibitors

❑ **Uses:** Stress ulcer prophylaxis. **Dose:** 1g / 6 hours taken orally before meals and at bedtime.

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❖ Side Effects:

1. Dry mouth, Indigestion & Constipation.
2. ↓ Absorption of food.
3. ↓Absorption of Drugs: Cimetidine, Phenytoin, Digoxin, Tetracycline, Fluoroquinolone Antibiotics & Ketoconazole.

3. Colloidal bismuth compounds:

❖ **Mechanism of action**

- In acidic pH, it forms a complex with protein at the ulcer base and forms a physical barrier.
- It↓ pepsin secretion and↑ secretion of endogenous PGs, mucus and bicarbonate
- It has **additional antimicrobial activity** against *H. pylori.*
- It is used as a component of quadruple therapy to heal peptic ulcers**.**

❖ **Adverse effects:** Black discoloration of mouth, tongue, teeth, and stools.

❖ **Dose:** 240 mg bid orally ½ hour before breakfast and at bedtime

4. Anti-Microbial To Eradicate H. pylori:

- H. pylori are gram -ve bacteria and present in about 70-90% of patients with peptic ulcer.
- For eradication of this infection use triple therapy or quadruple therapy.
- The common used antibacterial are:
- Clarithromycin. Of choice due to better acid stability & efficacy). (500 mg/12 hours)
- Amoxicillin. (500 mg/ 12 hours)
- Metronidazole (in patients allergic to amoxicillin) or Tinidazole

- **Triple therapy** for eradication of H. pylori: (2 antibacterial + PPIs)
- **For 14 days:** Clarithromycin + amoxicillin (or Metronidazole) + lansoprazole (15 mg/12h) or Omeprazole: (20 mg/12 hours)
- Followed by 4-6 weeks: PPI therapy to allow ulcer heal

- Quadruple therapy:

(2 antibacterial + PPIs or H2 blockers + bismuth)

- Administration of separated drugs is preferred than combination in one tablet.

Drugs used for Nausea -Vomiting

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Vomiting

- **Vomiting** protective reflex aiming at removal of toxins and irritant

- **Vomiting** may occur due to a variety of conditions:
  - GIT diseases, Pregnancy, Motion sickness, Meniere's disease, Severe pain (acute myocardial infarction) and renal colic, Stress and psychological disorders, Drugs: e.g. Cancer chemotherapy and radiotherapy.

❖ **Anti-Emetic drugs: act by inhibiting inputs to vomiting center;**

1. **D2 antagonists:** -metoclopramide – domperidone -promethazine
2. **5-HT3 receptor antagonists**: e.g. ondansetron, granisetron
3. **Antihistamines:** e.g. diphenhydramine, dimenhydrinate, meclizine.
4. **Anticholinergics:** e.g. hyoscine.
5. **Neurokinin-1receptor antagonists**: e.g. aprepitant
6- **Sedatives:** benzodiazepines e.g. lorazepam and diazepam.
7- Corticosteroids are potent antiemetics, with unknown mechanism.
   -Dronabinol is a cannabinoid acting on opioid receptors in CTZ.

1. D2-Antagonists:

- They act by blocking D2-receptors in CTZ so they are useful as anti-emetics except in motion sickness.

❖ **Preparation:**

❑ **Dual Anti-Emetic & Prokinetic agent:** Metoclopramide, Domperidone

- Blocks D receptor peripherally and centrally

○ **In CNS (central)**

- Metoclopramide: cross BBB, blockade of D_2 receptors in CTZ and, basal ganglia

- Domperidone: not cross BBB, blockade of D_2 receptors in CTZ and does not in basal ganglia → less side effect (EPS) but can cause hyperprolactinemia

○ **In GIT: Prokinetic:** ↑ G.I.T motility by D_2 antagonist & 5-HT4 stimulant → Ach release → ↑ gastric emptying & ↑ tone of lower esophageal sphincter (LES), and stimulates peristalsis. (Prokinetic agent)

Drugs used for Nausea -Vomiting

❖ Therapeutic uses

1. **All types of vomiting** except motion sickness: e.g. GIT disorders, drugs, radiation and Postoperative nausea and vomiting.

2. **Prokinetic in**: GERD, Gastric hypomotility (diabetic gastroparesis).

- Emergency evacuation of stomach before surgery or X-ray.
- Dose of metoclopramide: 10-15 mg before meals and at bed time orally or parentally.

3. Domperidone: Affects peripherally more than centrally, it is a preferred antiemetic in:
   - Children, (Not produces EPS).
   - vomiting induced by levodopa without affecting its anti-parkinsonian effect
   - Domperidone is less potent and less efficacious than metoclopramide

❖ Adverse effects:

1. Metoclopramide: Sedation, Parkinsonism, Hyperprolactinemia (Long-term use: infertility, menstrual irregularities and gynecomastia) and diarrhea.

2. Domperidone:
   - Diarrhea, headache, skin rashes, Hyperprolactinemia
   - Only used oral.
   - Parenteral administration is cardiotoxic

2. 5-HT3 receptor antagonists:

- Block 5-HT3 receptors in central (vomiting center & CTZ) and in the GIT
- Antianxiety action, Not effective in motion sickness

❖ **Preparation:** Given orally and IV

- **Short acting:** Ondansetron, granisetron, dolasetron.
- Granisetron & dolasetrone are more potent and longer acting than ondansetron.
- **long acting**: palonosetron

❖ **Therapeutic uses**

- 1st choice in post-operative and cancer chemotherapy induced vomiting (3 hours before surgery or drug

- 2nd choice in resistant cases of vomiting of pregnancy

❖ **Side effects**

- Dizziness, headache, constipation, short acting preparations cause cardiac arrhythmia due to K channel blocked.

- **NB:** Ginger contains natural $5HT_3$ blocker. It can be used as alternative antiemetic medication

Drugs used for Nausea -Vomiting

3. Antihistamines

They block H1 (also M1) receptors in vomiting center and vestibular system. They have sedative action.

- **Preparations:** Diphenhydramine, Promethazine, Meclizine, and Doxylamine.

❖ **Therapeutic uses: -Antiemetic**

- **1st choice, Motion sickness:** administrated 1 hour before travel (diphenhydramine).
- **Vomiting during pregnancy:** 2nd choice. given as oral tablets /8 hours (Doxylamine).
- Morning sickness (Meclizine)
- Meniere's disease (vertigo): promethazine, cinnarizine

❖ **Side effects**: Sedation, atropine like side effects

❖ **N.B.: Pyridoxine (vitamin B6):** 1st choice in vomiting of pregnancy either singly or in combination with Doxylamine or hydrocortisone

4. Anti-muscarinic drugs: Hyoscine tablets or transdermal patch or injection

❖ **uses: 2nd choice in** motion sickness: 1-3 hours before travel.

- Prophylactic against postoperative vomiting.

- **NB:** hyoscine butyl bromide, pirenzepine are anticholinergic drugs with no antiemetic effect because they do not pass blood brain barrier

5. Neurokinin receptor blockers:

- Blocks neurokinin receptors in vomiting center
- neurokinin receptors stimulated by substance P causing vomiting.

❖ **Preparations**: Aprepitant (Oral preparations) & Fosaprepitant: (I.V preparation, Prodrug to aprepitant).

❖ **Therapeutic uses: 2nd choice** in treatment of cancer chemotherapy induced vomiting in combination with corticosteroids and $5HT_3$ blockers

❖ **Side effects:** Fatigue and constipation. Interact with other drugs (Cyp450 inhibitors).

6. Other Anti-emetics:

1. **Glucocorticoids:** as dexamethasone and methylprednisolone.

- **2nd choice** in treatment of cancer chemotherapy induced vomiting in combination with other antiemetic agent.
- It may be combined with B6 = Cortigen B6) to control nausea and vomiting during pregnancy or children.

2. Benzodiazepines: diazepam, lorazepam, midazolam**,** used before cancer chemotherapy to reduce anxiety induced vomiting. Cause sedation, hypnosis, dependence and addiction

-

3. **Cannabinoids:** Nabilone and dronabinol.
- Used mainly in patients receiving cancer chemotherapy.
- Used if no response to other antiemetic due to serious **side effects**:
- **Side effects** Mood changes, addiction, hypotension, flushing, weight gain.

Prokinetic Drugs

- They are drugs that increase upper GIT motility and enhance gastric emptying.

1. **Metoclopramide, Domperidone**

2. **Itopride and Mosapride:**
- Prokinetic by activation of 5-HT4 receptors → release of Ach and stimulation of gastric motility and emptying.
- No D2 blocking action and accordingly it is not an antiemetic.
- Used in treatment of GERD in addition to PPIs.

3. **Muscarinic agonists**: bethanechol → increases GIT secretions as well as motility, used in non-obstructive paralytic ileus.

4. **Erythromycin:** has motilin-like action as it stimulates motilin receptors in GIT, used in diabetic gastroparesis.

Drugs used for Nausea -Vomiting

Choice of Antiemetics (depends on the cause of vomiting)

I. **Vomiting due to motion sickness**
- HI antagonists: e.g. diphenhydramine, dimenhydrinate, meclizine.
- Antimuscarinics: e.g. hyoscine (transdermal patch is better tolerated).

II. **Vomiting due to drugs, toxins**:
- D2 receptor antagonists e.g. metoclopramide and domperidone.

III. **Vomiting due to cancer chemotherapy** (combinations of antiemetics are used)
- 5-HT3 antagonists: ondansetron (1st choice, prophylaxis & treatment).
- Corticosteroids potentiate ondansetron.
- Neurokinin-1antagonists: aprepitant.
- Dronabinol (a cannabinoid).

IV. **Postoperative & post radiation nausea & vomiting**:
- Ondansetron - Metoclopramide.

V. **Nausea & vomiting of pregnancy**:
- Pyridoxine + Meclizine - doxylamine.
- Promethazine- metoclopramide – cortigen B6.

Diarrhea & Constipation Therapy

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Diarrhea

- ↑ frequency of defecation or watery stools more than 3-6 times daily, may be due to ↑ motility of the GI tract,↑ water secretions into the intestinal lumen and ↓ absorption of fluid → loss of electrolytes and water (**Diarrhea)**

❖ **Some causes of diarrhea**:

- **Infectious diarrhea:** bacterial, viral, fungal, protozoal, etc.
- **Malabsorption syndromes:** e.g. bile acid malabsorption
- **Hormonal (secretory) diarrhea (Increase motility):** Hyperthyroidism, hyperkalemia, Diabetic neuropathy, Diarrhea predominant irritable bowel syndrome
- **Inflammatory diarrhea:** caused by inflammatory bowel diseases
- **Drug induced diarrhea:** Oral penicillin, Colchicine, NSAIDS, Overuse of laxatives, magnesium salts, Laxatives, PG analogues.

❖ **Antidiarrheal:**

- Drugs that decrease motility of GIT and increase reabsorption of fluids from intestine.

❖ Treatment of Diarrhea

1. **Oral rehydration solution (ORS):** in conscious patients, IV fluids in severe cases (to correct fluid & electrolyte balance, more important than drugs).

2. **Specific antimicrobial therapy** against causative organisms:
   - ciprofloxacin 500 mg /12 h for 10 days Or cotrimoxazole, 2 tablets /12 hours. for most bacteria except Clostridium difficile

   - Metronidazole for Clostridium difficile, amoebiasis & giardiasis.

   - For cholera**:** 1st choice: doxycycline 500 mg /day & azithromycin 500 mg/day for pregnant and children

3. **Symptomatic treatment**: antidiarrheal agents.

Drugs used for Diarrhea

❑ Antidiarrheal agents

1. Anti-motility drugs: Loperamide , Diphenoxylate **(opioid-related)**

❖ Mechanism of action:

- Stimulate opioid receptors (μ receptors) in intestinal mucosa1→ ↓ acetylcholine release → ↓ intestinal motility and secretions.
- Spasmogenic effect with diphenoxylate.
- Diphenoxylate is:
  - co-administrated with atropine (Lomotil)® to prevent abuse by addicts (synergism and less side effects).
  - At therapeutic doses they do not cross BBB (act only peripherally).
- Loperamide has little side effects on CNS (does not BBB penetration).

❖ **Therapeutic used**: in non-inflammatory & traveler's diarrhea, and drug induced diarrhea.

- **Side effects:** constipation, abdominal cramps, drowsiness and dizziness.
  - Tolerance. (not used for long time = Diphenoxylate)

- **Contraindicated**: infection diarrhea (presence fever) and bloody diarrhea, inflammatory diarrhea because they prevent removal of invading organisms, also in children.

Drugs used for Diarrhea

❑ **Parasympatholytic**: Atropine & propantheline.

- Inhibit muscarinic receptors.
- Propantheline is more selective action on GIT and less penetration for CNS comparing to atropine. (more polar)
- **Side effects** include anticholinergic effects.

2. Toxin adsorbents: Kaolin, pectin, charcoal, bismuth subsalicylates

- They remove toxins, increase stool viscosity and form mucosal cytoprotective
- Decrease stool softness.
- Have weak antidiarrheal effect.
- Bismuth subsalicylate is also used in Traveler's diarrhea (due to E. coli)
- Interfere with the absorption of other drugs.

Drugs used for Constipation

Drugs used for Constipation

Constipation

- Infrequent bowel movement less than 3 /week (normal 3-12 /week)
- straining or pain, sensation of incomplete evacuation, hard stools.

❖ Some causes of constipation:

- Low fiber diet & fluid intake.
- Old age.
- Lack of physical exercises.
- Drugs (as opioids, anticholinergics, diuretics, tricyclic antidepressants & iron preparations).
- GIT diseases (as irritable bowel syndrome).
- Hormonal disturbances (as hypothyroidism).
- Neurogenic disturbances. (as stress, parkinsonism & depression).
- Pregnancy & Increase drinking tea & coffee.

❖ Types of anti-constipation drugs

- **Laxatives**: mild effect →Drugs that evacuate formed stools from rectum (e.g. Bulk-forming, Stool surfactant)
- **Purgatives:** moderate effect → loose stool (e.g. Osmotic drugs)
- **Cathartics**: strong effect → Drugs that evacuate unformed stools from entire colon (e.g. Stimulant, Chloride channel activator)

Drugs used for Constipation

❖ **Treatment of constipation:**

A) Non-pharmacological therapy:

- ↑ fluid intake to 6–8 glasses of water per day: **stool softness**.
- ↑ dietary fiber to 20–30 g/day (fruits, vegetable and cereals): **bulk-forming**
- ↑ exercise: **stimulate intestinal activity**.
- Avoidance of delay response to desire for defecation.

B) Pharmacological therapy:

- Drugs (Purgatives, Laxatives) are commonly used for increase the lower GIT motility and enhanced intestinal evacuation
- These drugs can be classified on the basis of their mechanism of action:

1. **Bulk-forming laxatives**: Oral Methyl cellulose, bran- Carboxymethyl cellulose .

- **Mechanism of action**
- They are non-digestible fibers, hydrophilic colloids → retain water in the gut and↑ bulk of intestinal contents → activation of stretch receptors → stimulation of peristalsis.
- Bulk forming laxatives should be used with large amounts of water.
- Suitable & safe in chronic constipation of elderly, pregnancy, renal and hepatic patients.
- **Efficacy:** Moderate, slow (1-3 days)
- **Side effects:** abdominal distension – ↓ absorption of some drugs (e.g. digoxin), intestinal obstruction.

2. Stool surfactant laxatives (softeners):

- Surface active agents → lower the surface tension of the stool to allow mixing of aqueous and fatty substances → softening the stool and permitting easier defecation.

a) Docusate sodium (oral or enema).

- ↑ water entry into stools by decreasing its surface tension.
- **Onset of action**: 1-3days (orally), 5-20 minutes (rectal).
- **Uses:**. Constipation with hard stool, prophylaxis rather than acute treatment
- Dose: 200 mg at night.
- **S.E:** Intestinal obstruction.

b) Liquid paraffin: Paraffin Oil

- Lubricates hard stools leading to softening and easy evacuation.
- Acts after 10-12 hours.
- **Useful** in Chronic Constipation. Constipation with anal fissures, After anal surgery and in patients with cardiac disease
- Dose 15 - 30 ml at night
- **S.E:** Bad taste, Anal pruritus. (with long term use), ↓ Absorption of fats (steatorrhea), some drugs and fat soluble vitamins (A, D, E & K),.

-

Drugs used for Constipation

c) Glycerin suppositories.

- It has osmotic, stimulant and lubricate effects
- Given rectally. (Absorbed from GIT)
- Rapid action in about one hour.
- Use for acute constipation.
- Suitable for children and elderly people.

3. Osmotic agent: Mg sulfate & Na salts – Lactulose

- Non absorbable salts → retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

a) Saline: Mg sulfate & Na salts.

- The most powerful and rapid-acting laxatives
- Producing defecation in about one hour (Potent, rapid 1-3 hours).
- They should be avoided in young children and patients with renal failure or cardiac diseases

- **S.E:** Colic & distension, bad taste, abortion.
- Mg & Na salts (saline laxatives) may be absorbed systemically and produce hypermagnesemia and hypernatremia especially in patients with renal failure.

Drugs used for Constipation

b) **Lactulose:** (Duphalac)®

- A disaccharide of fructose and galactose → degraded in colon by bacterial flora to lactic acid and acetic acid → increases osmotic pressure, → fluid accumulation into the lumen , colon distension, soft stools, and defecation

- **Uses :**

- Constipation. (Safe and used for all ages and pregnancy).
- In hepatic encephalopathy to reduce blood ammonia levels .
- **Onset of action:** 1-2 days **Dose:** 10-20 g 3-4 times daily.
- **S.E:** abdominal discomfort.

4. Stimulant laxatives: Castor oil – Senna – Bisacodyl

- **Mechanism of action:**

- They produce inflammation (irritation) of the intestinal mucosa leading to:
  - Accumulation of water and electrolytes in the gut lumen.
  - Direct stimulation of peristalsis by their irritant effect

- **Side effects:**

- Colic, dehydration, Tolerance due to damage of mucosa and nerve endings
- Dependence due to decrease normal peristalsis

Drugs used for Constipation

1. **Castor oil:**

- Hydrolyzed in intestine by lipase and bile to ricinoleic acid which is very irritant → ↑ peristalsis.
- Potent fast effect. about 2-6 hours.
- **Uses** for total colonic evacuation before surgery or radiologic.
- **Contraindicated** in pregnancy and menstruation.

2. **Senna:**

- Widely used stimulant laxative.
- Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides.
- Taken orally, senna causes evacuation of the bowels within 8 to 10 hours.
- Uses short term acute constipation.
- Uses for total colonic evacuation such as before surgery or radiologic.
- Senna + docusate, → useful in treating opioid-induced constipation.

Drugs used for Constipation

3. Bisacodyl:

- Available as suppositories and enteric-coated tablets, bisacodyl is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon**.**
- Uses for acute and chronic constipation (safe for pregnancy).
- Uses for total colonic evacuation such as before surgery or radiologic.
- Given once daily at bed time
- Onset of action: 6-10 h (orally) and 30-60 minutes (rectally).

5. Chloride channel activators: Lubiprostone

- **Mechanism of action:**
- It acts by activating chloride channels → ↑ fluid secretion in the intestinal lumen → eases the passage of stool and causes little change in electrolyte balance.
- **Used**: treatment of chronic constipation and irritable bowel syndrome (IBS) with predominant constipation, because tolerance or dependency has not been associated with this drug

Drugs used for Constipation

❖ Therapeutic uses of laxatives:

1. Constipation
   - Intermittent constipation → best treated by high fiber diet, plenty of fluids & exercise.
   - treat constipation with low bulk stool → bulk-forming or osmotic agents,
   - Constipation with low frequency of defecation, gut evacuation before surgery or radiology → stimulant agents,
   - Constipation with hard stool → stool softeners

2. After anal surgery → lubricants (parrafin oil).
3. Hepatic encephalopathy → lactulose.
4. Ingested poison & taenia solium treatment → MgS04.
5. To avoid straining during defecation in patients with cardiovascular disease → docusates or bulk laxatives.
6. Constipation with irritable bowel syndrome → Cl channel activator ,
7. To treat constipation in children and pregnant women → lactulose, bulk forming laxatives.

N.B:

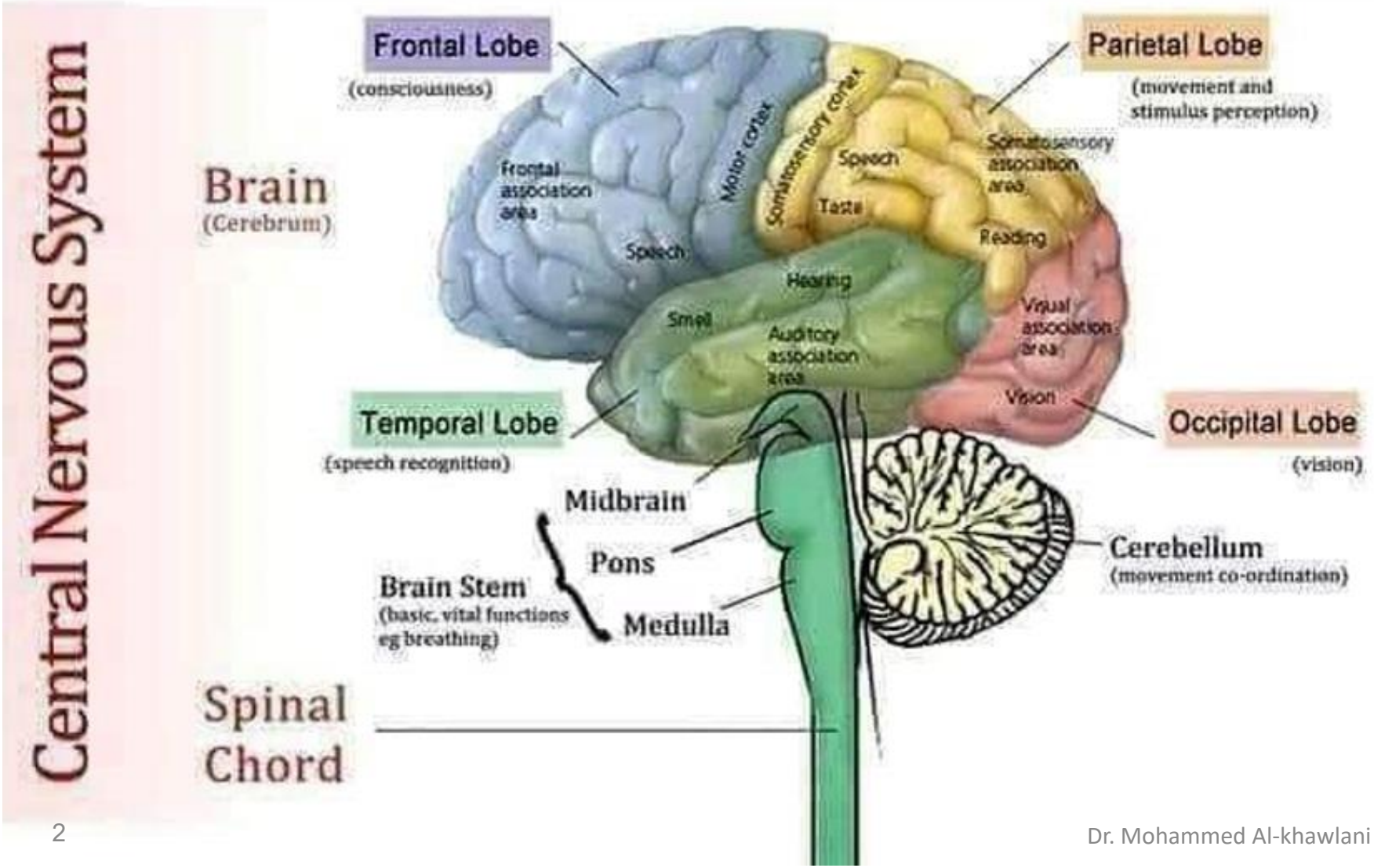
- laxatives should not be used for prolonged duration to avoid laxative dependence
- Stimulant laxatives should be taken on empty stomach to avoid vomiting.
- Bulk forming laxatives & Osmotic should be used with large amounts of water.
- Avoid stimulant laxatives in treatment of irritable bowel syndrome because they increase colic.

Central Nervous System (C.N.S), sedative-hypnotics

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

The Nervous System



❖ Neurotransmission in CNS:

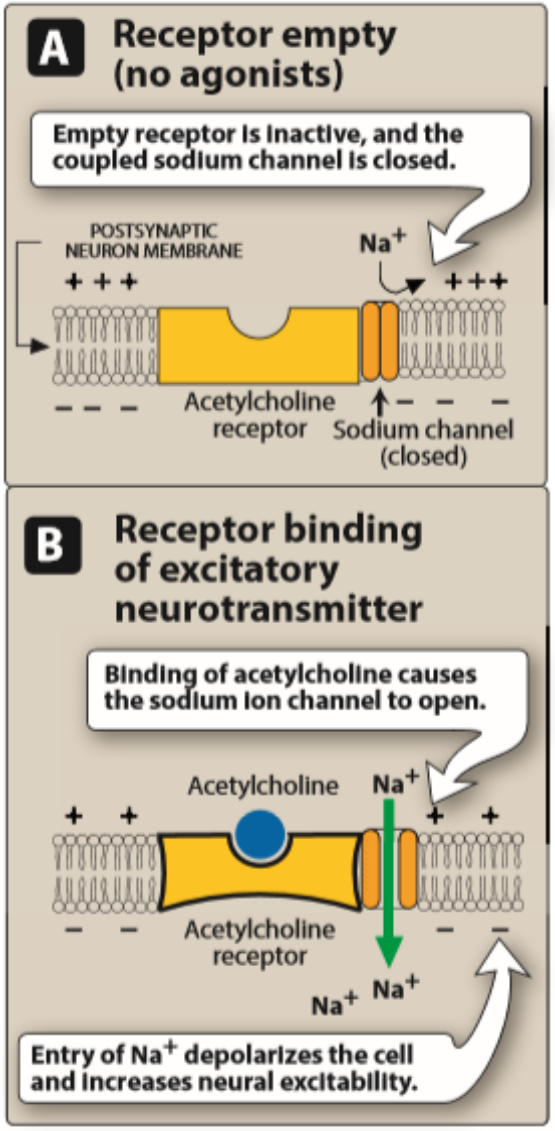
Transmitter	Anatomical Distribution	Receptor Subtypes	Receptor Mechanisms
Acetylcholine	Cell bodies at all levels, short and long axons	Muscarinic, M_1; blocked by pirenzepine and atropine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		Muscarinic, M_2; blocked by atropine	Inhibitory; ↑ K^+ conductance; cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D_1; blocked by phenothiazines	Inhibitory; ↑ cAMP
		D_2; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	$Alpha_1$; blocked by prazosin	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$Alpha_2$; activated by clonidine	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
		$Beta_1$; blocked by propranolol	Excitatory; ↓ K^+ conductance; ↑ cAMP
		$Beta_2$; blocked by propranolol	Inhibitory; ↑ electrogenic sodium pump
Serotonin (5-hydroxytryptamine)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$; buspirone is a partial agonist	Inhibitory; ↑ K^+ conductance
		$5\text{-}HT_{2A}$; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG

		5-HT_3; blocked by ondansetron	Excitatory; ↑ cation conductance
		5-HT_4	Excitatory; ↓ K^+ conductance; ↑ cAMP
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	$GABA_A$; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl^- conductance
		$GABA_B$; activated by baclofen	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance
Glutamate, aspartate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine, ketamine, and memantine	Excitatory; ↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP
			Excitatory (postsynaptic); ↓ K^+ conductance; ↑ IP^3 and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl^- conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: μ, δ, κ	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP

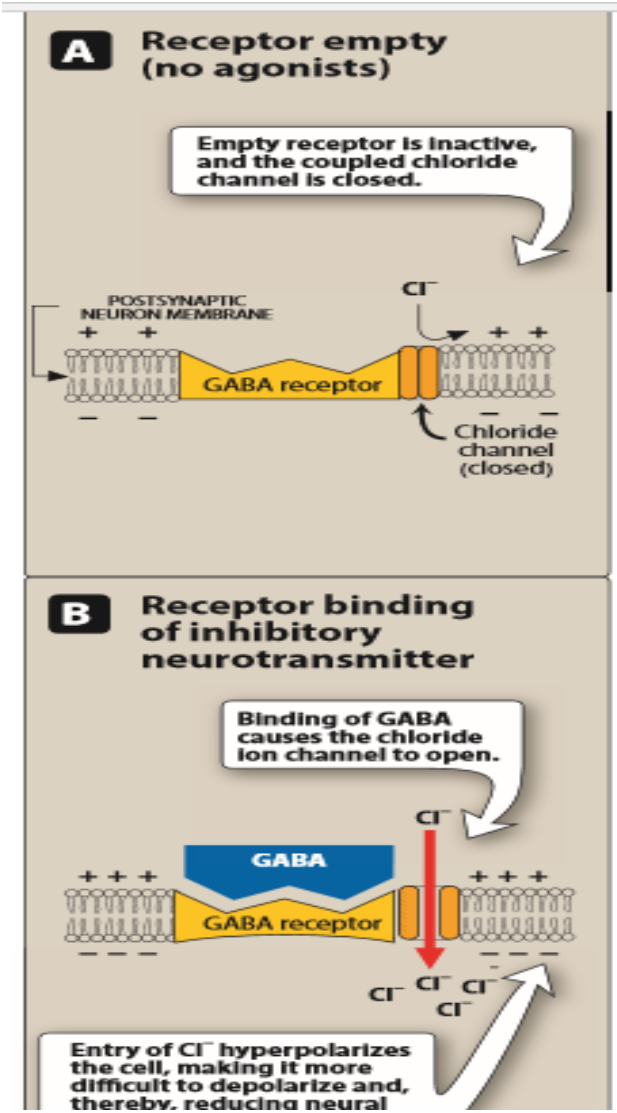
- In normal situation, there is a balance between the excitatory and inhibitory neurotransmitters.

- **Excitatory postsynaptic potential (EPSP)** When an excitatory neurotransmitter binds and interacts with the specific receptors on the postjunctional membrane, the membrane permeability to cations increases

- **Inhibitory postsynaptic potential (IPSP)** When an inhibitory transmitter binds and interacts with specific receptors on postjunctional membrane, the membrane permeability to K+ or Cl– increases.



1- Excitatory pathway


A
Receptor empty (no agonists)
Empty receptor is inactive, and the coupled chloride channel is closed.
POSTSYNAPTIC NEURON MEMBRANE
Cl−
GABA receptor
Chloride channel (closed)
B
Receptor binding of inhibitory neurotransmitter
Binding of GABA causes the chloride ion channel to open.
GABA
GABA receptor
Cl−
Entry of Cl− hyperpolarizes the cell, making it more difficult to depolarize and, thereby, reducing neural

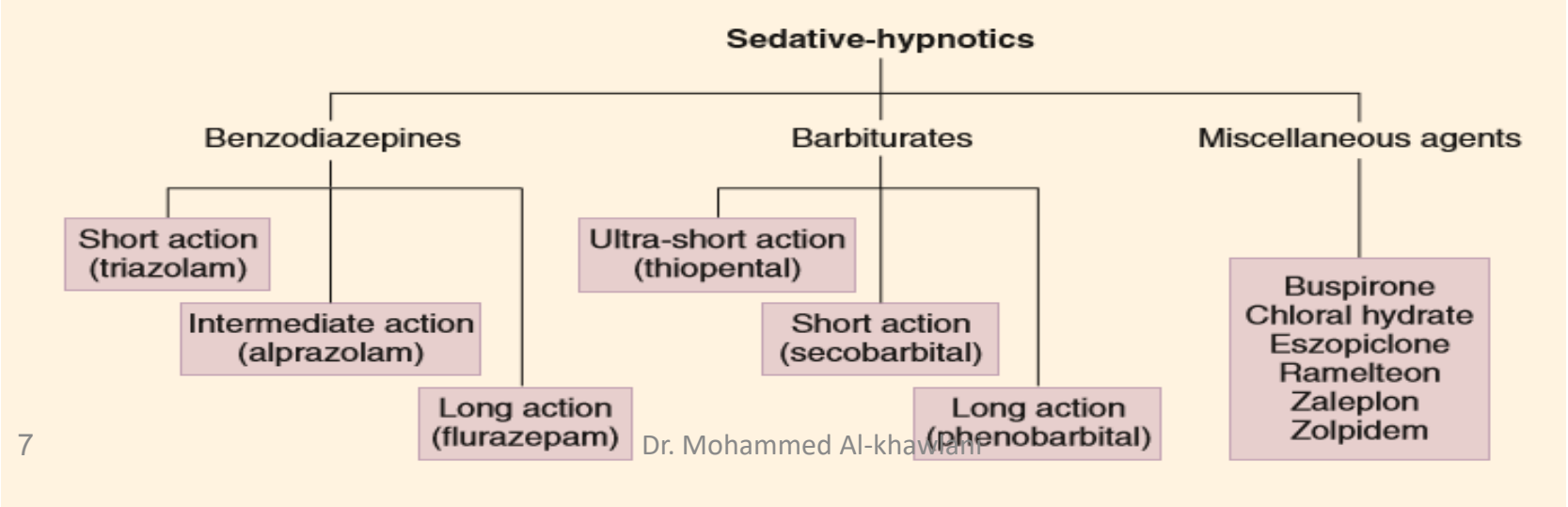
2- Inhibitory pathway.

Sedative & hypnotics

❖ Sedative -Hypnotic Drugs

- **Sedative:** The drug that reduces anxiety and exerts a calming effect. (anxiolytic effect)
- **Hypnotic**: The drug that induces sleep.
- Sedatives – hypnotics drugs → S.D. (Sedative) & in large dose (Hypnotic).

- Barbiturates (Bb) → Bb-GABA agonist →↓ REM, HME induction, ↓ RC & No antidote
- Benzodiazepines (Bz) → Better than barbiturates
- Zolpidem, Zaleplon, Zopiclone → Non-Bz → Bz-GABA agonists
- Melatonin receptor agonists (MT1 & 2)→↑ REM & ↓ latency period to fall asleep.



1- Benzodiazepines: (BDZs)

❖ Classification of BDZs:

- **Long-acting (Half life is>24 h):** produce day time sedation & drowsiness.
  e.g.- Diazepam (Valium)®, Clonazepam (Rivotril)® - Clorazepate - Flurazepam.

- **Intermediate-acting (Half life is 12 h):** Slowly absorbed → Delayed onset → Not useful to initiate sleep But to maintain it.
  e.g.: - Alprazolam (Xanax)® - Lorazepam - Temazepam - chlordiazepoxide - Estazolam

- **Short-acting (Half life is <12 h):** Rapid oral absorption → Rapid onset →Useful to initiate sleep.
  e.g.: Midazolam - Oxazepam- Triazolam

❖ Pharmacokinetics

- BDZs are lipophilic, rapid oral absorption & distribute and penetrate into the CNS.
- Metabolized in the liver to active compounds.
- Excreted in urine as glucuronides or oxidized metabolites and in breast milk
- All BDZ cross the placental barrier & may depress the CNS of the newborn if given before birth.

Sedative & Hypnotics

❖ **Mechanism of action:** - Bind to the BDZs site on GABAA receptors → opening Cl- channels →↑ Cl- influx → enhance hyperpolarization → inhibit neuronal excitability.

❖ **Actions of BDZ:**

- **Inhibition of central nervous system in the following order:**
  - Inhibition of limbic system → relieve of **anxiety** (anxiolytic – minor tranquilizer)
    → **depression**

  - Inhibition of reticular formation→ **Sedation** (low dose**) - hypnosis** (high dose)- **anesthesia** action

- **Inhibition of motor activity** → anticonvulsive action, Skeletal muscle relaxation and Ataxia

- **Amnesia**: (temporary impairment of memory.

- Inhibition of satiety ---**overeating**

- Large doses causses slight hypotension , cardiac depression only in very large doses or patients with cardiac diseases (Inhibition of autonomic vital centers)

❖ Therapeutic uses of BZ

1. **Antianxiety (anxiolytic) effect**: (clonazepam, lorazepam , diazepam & Alprazolam).

2. **Sleep disorders & insomnia (hypnotic in large doses):**.
   - Temazepam (frequent wakening).
   - Triazolam (difficulty in going to sleep).

   →↓ latency period to start sleep, ↑total sleep time, prolongation of NREM and ↓REM

3. **Anticonvulsant** (**Antiepileptic agent, seizures)**: Diazepam (faster), lorazepam (longer), clonazepam (stronger), clobazam. have selective anticonvulsant effect.

4. **Adjuncts to Anesthesia**, **Preanesthetic medication,:** Midazolam (short acting) to facilities amnesia in minor operative procedures and endoscopies. diazepam, lorazepam, midazolam are used IV in anesthesia

5. **Muscle relaxant:** Diazepam
   Used in skeletal muscle spasms,

6. To treat alcohol-withdrawal symptoms: chlordiazepoxide, diazepam).

Adverse effects

- Due to skeletal muscle relaxation → **ataxia, Sleep apnea syndrome** due to excessive relaxation of respiratory muscles
- Due to decrease duration of REM → **Antigrade amnesia** (loss of memory during drug intake)
- Due to excessive sedative effect → **drowsiness** after stoppage of long acting benzodiazpines
- **Tolerance, dependence and addiction**. (high doses for long time) is treated by gradual withdrawal of the drug
- Sudden withdrawal after chronic use causes symptoms like tremor, insomnia, restlessness, nervousness
- Depression except alprazolam & overeating and weight gain
- Overdose toxicity leading to mild cardiac and respiratory depression treated by: flumazenil (benzodiazepine receptor antagonist).

NB: BDZs potentiate the action of other CNS depressants

Flumazenil (Benzodiazepine Antagonist) :

- It is a GABA-receptor antagonist that can rapidly reverse the effects of BZ.
- Has a short duration of action.
- Given intravenously as an **antidote** in case of Benzodiazepine poisoning.
- May cause dizziness, nausea, vomiting & agitation.

Group	Drug	MOA	CU	Route	Onset	Duration	Metabolism Remarcks
Benzodiazepines	Midazolam	GABA potentiation	IV anesthetic	IV	fast	< 6 h	
	Triazolam		insomnia	Oral			
	Lorazepam		anxiety, insomnia, epilepsy, and anesthesia	O/P	slow	12-18 h	conjugated with glucuronide
	Oxazepam		anxiety, insomnia	Oral			conjugated with glucuronide
	Temazepam		insomnia				
	Alprazolam		anxiety, depression		fast	24 h	
	Nitrazepam		insomnia, epilepsy		=		
	Chlordiazepoxide		anxiety, insomnia	O/P	slow	24-48 h	metabolized into oxazepam
	Clonazepam		anxiety, epilepsy	Oral	fast		
	Clorazepate		anxiety (prodrug)				metabolized into oxazepam
	Diazepam		anxiety, insomnia, epilepsy, and anesthesia, addiction	O/P/R			metabolized into oxazepam
	Flurazepam		Anxiety			40-100 h	
	Flumazenil	BDZ-antagonist	BDZ overdose	IV	fast	1 hour	

2- Barbiturates:

- They are nonselective CNS depressants.
- They are derivatives of barbituric acid.
- It is a narrow spectrum antiepileptic drug .It is contraindicated in petit mal epilepsy because it may precipitate generalized convulsion(transform petit mal to grand mal).
- They were used for treatment to sedate patients or to induce and maintain sleep.
- Today, they have been largely replaced by the benzodiazepines, because BDZs are:

  - a wide therapeutic index. Safer than barbiturates on R.C. & C.V.S.
  - Less REM → Less hangover & Less rebound paradoxical sleep.
  - NO Hepatic Microsomal Enzyme Induction
  - Less tolerance, Less dependence and Less drug interactions.
  - Available specific antidote = Flumazenil.

❖ Classifications and example of barbiturates:

- **Long-acting (1-2 days)** : Phenobarbital
- **Short-acting (3-8 hours)** : Secobarbital, Amobarbital
- **Ultra-short acting (20 minutes)** : Thiopental (Not hypnotic, I. V. anesthesia).

❖ Pharmacokinetics

- Absorbed orally & distributed widely throughout the body.
- All barbiturates redistribute in the body, from the brain to the splanchnic areas, to skeletal muscle, & to adipose tissue.
- They readily cross the placenta & can depress the fetus.
- Metabolized in the liver. – Inactive metabolites excreted in urine.

❖ Mechanism of action: –

- Barbiturates have GABA-facilitatory action → they potentiate inhibitory effects of GABA.
- Barbiturates can block excitatory glutamate receptors.

Pharmacological actions

1. **Depression of CNS:**
   - Sedative action BUT → Drowsiness
   - Hypnotic action BUT Abnormal sleep → ↓REM
   - Amnesia.
   - General anesthesia, especially Ultra-short acting barbiturates.
   - Anti-Convulsant (ALL barbiturates treat ALL convulsions except petit mal epilepsy)

2. **Respiratory depression**:
   • Overdosage lead to respiratory depression & death.
3. **Hepatic Microsomal Enzyme induction**. → increase metabolism and decrease effect of
   - The same drug (barbiturates) → tolerance and Other drugs (drug interaction)
4. Large dose causes severe CNS inhibition → coma , severe hypotension and mild respiratory depression
5. Inhibition of folic acid activating enzyme (folate reductase) → megaloplastic anemia
6. Inhibition of vitamin D activating enzyme → osteoporosis.

❖ Therapeutic uses

1. **General anesthesia (GA):** Ultra-short-acting barbiturates (thiopentone) are used for the induction of GA. but have largely been replaced by other agents.

2. **Sedation and hypnosis**:
   Low dose: used in anxiety.
   High dose (hypnosis): Phenobarbital (Patients who get up very early), Secobarbital (Anxious unable to start sleep), Amobarbital (used for Interrupted sleep).

3. **Anticonvulsant:** Phenobarbitone has anticonvulsant effect and is used in the treatment of status epilepticus and generalized tonic–clonic seizures (GTCS).

❖ Adverse effects

- Drowsiness, nausea & vertigo.
- Drug hangover. (abnormal sleep and tiredness after waking)
- CNS & respiratory depression. (in high doses)
- Tolerance, Physical and psychological dependence develops on repeated use.
- Withdrawal is much more severe than that associated with opiates & can result in death.

- Barbiturates induce the hepatic metabolism of many drugs as warfarin, tolbutamide and corticosteroids.

3- Other anxiolytics and hypnotics

1. Melatonin receptor agonists

❖ **Preparation**: Ramelteon

- Melatonin is a hormone secreted from pineal body to regulate circadian clock (internal time) It is secreted from 8 pm to 5 am to inhibit reticular formation.
- Other functions includes anti-oxidant , anti-neoplastic , regulation of secretion of mood.
- They act by stimulation of melatonin(MT1 & 2) receptors → Rapid onset of sleep with minimal rebound insomnia after sudden stoppage or tolerance (withdrawal symptoms)

❖ **Therapeutic uses :**

- It is used as hypnotic in cases of:

- Jet lag (disturbance in sleep during travelling in destinations with different time zone). It is orally administrated at the night of departure and repeated for 3 days after

- Insomnia in old age characterized by difficulty falling asleep (increased sleep latency)

- Dose: 8 mg/ day 30 min. before sleep.

❖ **Side effects:** include dizziness, fatigue, and somnolence, increase prolactin levels

2. Newer hypnotics (Non benzodiazepine, agonists of benzodiazepine receptors)

❖ **Preparation:** zolpidem, zaleplon, zopiclone, eszopiclone.

- Absorption after oral administration, Extensive hepatic metabolism by microsomal enzymes and glucurinde conjugation into inactive metabolites. Metabolism is delayed in cases of hepatic impairment .
- They have very rapid onset of hypnosis with few amnestic effects or hang over than benzodiazepines .
- No tolerance, withdrawal syndrome, dependence.
- No anti-anxiety action, muscle relaxation or anticonvulsant.

- Zopiclone is orally effective and is used for short-term treatment of insomnia. It produces near-normal sleep like BZDs.

- Zaleplon: It is useful in sleep-onset insomnia (difficulty in in sleep initiation).. It is the shortest-acting non-BZD hypnotic (3h, duration of action).

- zolpidem , Eszopiclone: It is used orally for long-term treatment of insomnia (frequent wakening, chronic insomnia).

- **Side effects**: Less toxic than benzodiazepines; nightmares, amnesia, headache, GI upset, dizziness, and daytime drowsiness.

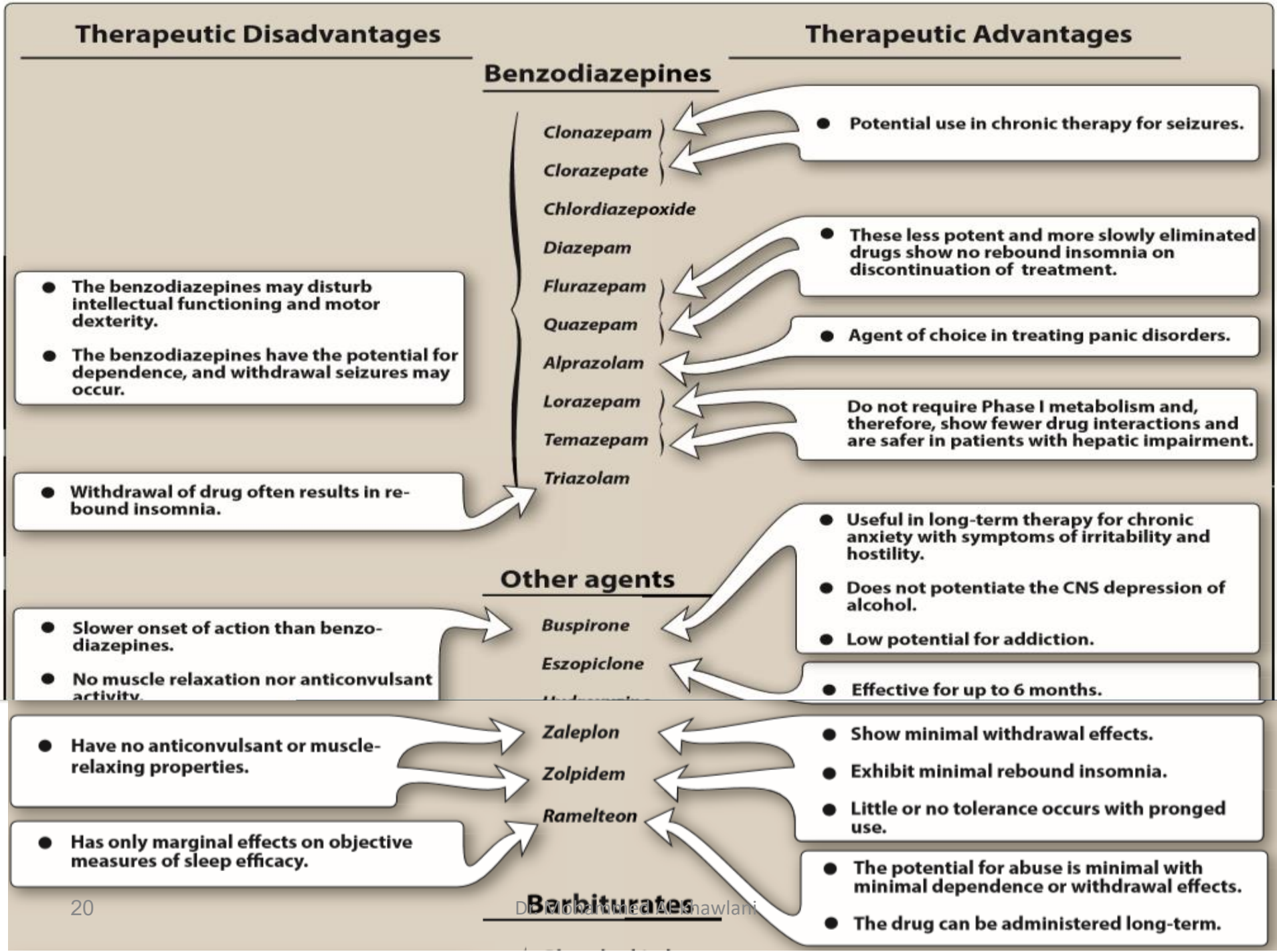
3. Buspirone:

- Buspirone has selective anxiolytic effects,.
- Buspirone relieves anxiety without causing marked, hypnotic, or euphoric effects.
- Unlike benzodiazepines, the drug has no anticonvulsant or muscle relaxant properties..
- Little or no addiction or withdrawal syndrome on sudden stoppage of the drug. Favorable effect on old age
- The anti-anxiety effect is slow onset (7 days). It is effective in chronic but not acute anxiety.
- M.O.A: It acting as a partial agonist at brain 5-HT1A receptors in limbic system with no effect on that of reticular formation.
- C.U: The drug is used in generalized anxiety states& in anxiety with depression.
- S.E.: Peripheral and central sympathomimetic effect leading to tachycardia and hypertension and nervousness which is increased by concomitant administration with MAO inhibitors.

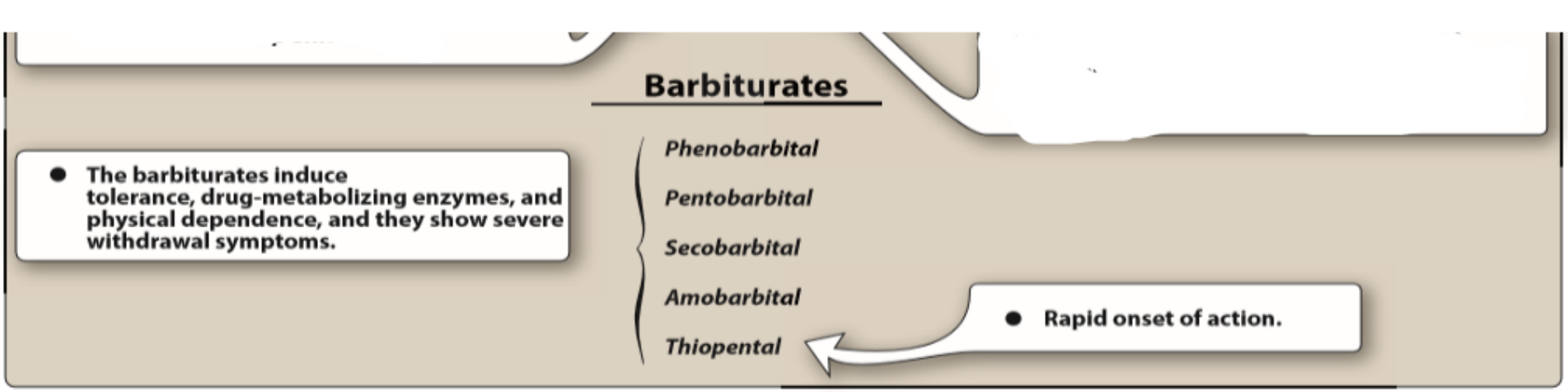
4. Antihistamines

❖ **Preparation**: diphenhydramine, doxylamine, promethazine

- **Actions**: Sedative-hypnotic, Antihistaminic, Anticholinergic & Antiemetic.
- No drug dependence.
- **C.U.:** treating mild types of situational insomnia.
- **S.E:** anticholinergic effects that make them less useful than the benzodiazepines and the nonbenzodiazepines.
- Some sedative antihistamines are marketed in numerous over-the-counter products


Therapeutic Disadvantages
Therapeutic Advantages
Benzodiazepines
Clonazepam
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Alprazolam
Lorazepam
Temazepam
Triazolam
Potential use in chronic therapy for seizures.
These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
Agent of choice in treating panic disorders.
Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.
The benzodiazepines may disturb intellectual functioning and motor dexterity.
The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.
Withdrawal of drug often results in re-bound insomnia.
Other agents
Buspirone
Eszopiclone
Zaleplon
Zolpidem
Ramelteon
Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
Does not potentiate the CNS depression of alcohol.
Low potential for addiction.
Effective for up to 6 months.
Slower onset of action than benzo-diazepines.
No muscle relaxation nor anticonvulsant activity.
Have no anticonvulsant or muscle-relaxing properties.
Has only marginal effects on objective measures of sleep efficacy.
Show minimal withdrawal effects.
Exhibit minimal rebound insomnia.
Little or no tolerance occurs with pronged use.
The potential for abuse is minimal with minimal dependence or withdrawal effects.
The drug can be administered long-term.
Barbiturates

Dr. Mohammed Alshawlani


Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
Thiopental
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.
Rapid onset of action.

Anxiolytics (Antianxiety drugs)

Minor tranquillizers = Anxiolytics =Antianxiety drugs: These drugs are used in treatment of anxiety disorders as panic disorders, phobias, and stress disorders. Examples include Benzodiazepines (e.g. Diazepam), Buspirone.

Rapidly acting
- -Lipophylic B blockers
- -Benzodiazpines

Slowly acting
- -Antidepressant drugs
- -Buspirone
- -Antiepileptic durgs

1-Lipophylic B blockers(Propranolol)

Advantages: rapidly acting
-relieve physical manifestations of anxiety

Disadvantages: -No effect on emotional manifestations of anxiety
-Night mares
-Sedation

2-Benzodiazpines

Advantages:-Rapidly acting
-Very potent
-Few side effects

Disadvantages:-Sedation , amnesia
-Decrease cognitive function
-Addiction , insomnia on sudden withdrawal

3-Antidepressant drugs

Advantages: Potent effect
-Relieves emotional response to anxiety

Disadvantages: -Delayed action after2-4 weeks
-They cause initial exacerbation of anxiety
-Suicidal tendency

4-Antiepileptic drugs (Gabapentine)

-It stimulates GABA A receptors.

Advantages :Potent

-It is used to prevent anxiety due to Withdrawal of addictive drugs

Disadvantages: -Hepatotoxic

-Similar to benzodiazpines

Buspirone = partial 5HT1A

initial increase in 5HT release

-Initial exacerbation in anxiety

Advantages:-Potent

-Non sedative

-No addiction.

-No effect on memory

Late decrease in 5HT release

Delayed anti-anxiety effect.

Disadvantages:-Delayed onset

-Initial exacerbation of anxiety

-No effect on anxiety due to drug withdrawal

-Hypertension due to metabolism to catecholamine like substances

Choice of antianxiety drugs

Acute anxiety is treated by rapidly acting antidepressants : Lipophylic B blockers (propranolol) or intermediate or short acting benzodiazepines (lorazepam & alprazolam).

Long term therapy of chronic anxiety:

Benzodiazepines for 4 weeks + antidepressants : selective serotonin reuptake inhibitors (fluoxetine) for young persons or selective norepinephrine reuptake inhibitors (venlafaxine) in old persons.

Treatment of affective disorders (Depression & Mania & Bipolar disorder)

Treatment of Affective disorders

❖ **Affective (Mood) disorders** are characterized by primary changes in mood with no disturbance in thoughts .They have the following clinical types:

1- **Depression** is a very common clinical condition associated with feeling of sadness, loss of interest, self neglect, anorexia, sleep disturbances, suicidal feelings in severe cases, etc.

2- **Mania** which is characterized by opposite manifestations of depression i.e.:

- Over self-confidence.
- Increase physical activity.
- Increase speech and flow of thoughts.
- Irritability.

3-Bipolar affecting disorder in which depression is alternated by mania

Antidepressant drugs

Classification Of anti-Depressants:

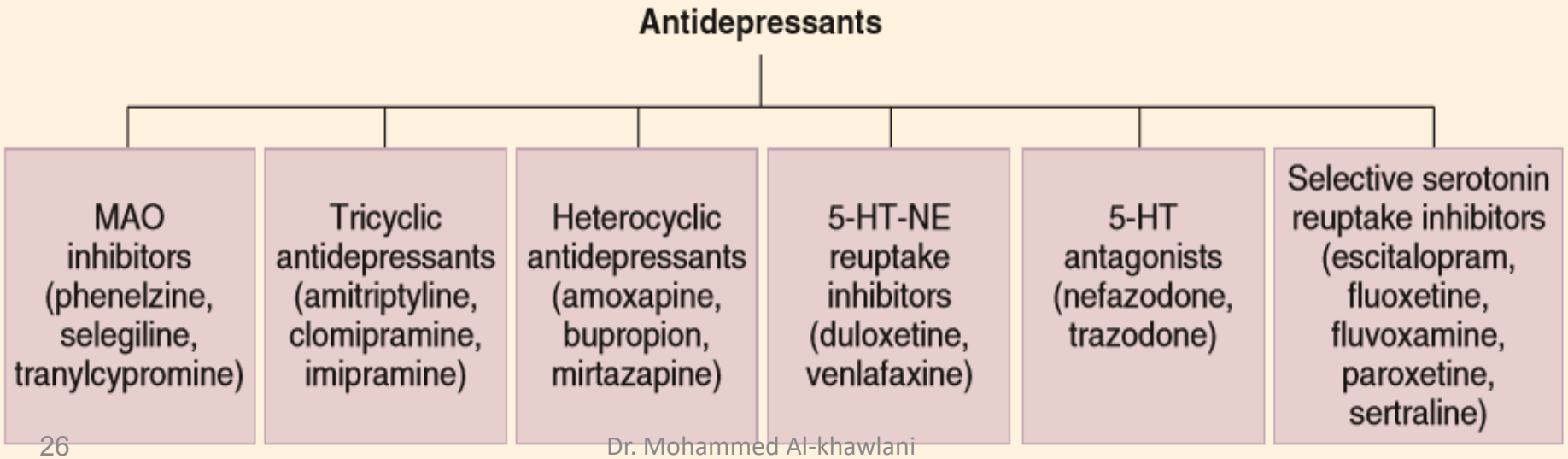
1-Monoamine reuptake Inhibitors:

a-Tricyclic Antidepressants: → decrease Reuptake of Both NA & 5-HT Examples:

b-Selective Serotonin Reuptake Inhibitors (SSRI).

2-Mono-Amine Oxidase Inhibitors (MAOI) e.g. Tranylcypromine ..

3-Other.s e.g. Mianserine → Presynaptic α2 & 5-HT Blocker → ↑ Release of NA, 5-HT.


Antidepressants
MAO inhibitors (phenelzine, selegiline, tranylcypromine)
Tricyclic antidepressants (amitriptyline, clomipramine, imipramine)
Heterocyclic antidepressants (amoxapine, bupropion, mirtazapine)
5-HT-NE reuptake inhibitors (duloxetine, venlafaxine)
5-HT antagonists (nefazodone, trazodone)
Selective serotonin reuptake inhibitors (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)

Antidepressant drugs

1- Tricyclic antidepressants: (TCAs)

Preparation:

- **Tertiary amines**: Imipramine , amitriptyline ,clomipramine ,doxepin , trimipramine

- **Secondary amines** : Nortriptyline , protriptyline, desipramine.

- **Tetracyclic:** Maprotiline, amoxapine

Pharmacokinetics

- lipophilic nature, absorbed orally (Given orally once daily preferred at night).
- They are highly bound to plasma proteins, widely distributed in tissues (CNS & placenta).
- In the liver tertiary amines are metabolized to secondary mines then they are inactivated by conjugation with glucurionic acid → Inactive metabolites, excreted mainly in urine as inactive.
- They have slowly acting. The onset of antidepressant effect starts after 3-4 weeks
- They have prolonged effect .Their antidepressant effect persists after 3-4 weeks of discontinuation
- Low therapeutic index.

Antidepressant drugs

Mechanism of action:

- **Immediate action:** Inhibit neuronal reuptake of NE and 5-HT →↑ concentration in synaptic cleft → **antidepressant effect.**

- **Delayed action:**
  - Inhibition of presynaptic inhibitory α2 & 5HT1
  - Block α1, H1, 5-HT, and M receptors → **unwanted effects.**

❖ Actions of Tricyclic Antidepressants

- **Anti-Depressant Effect:** antidepressant effect starts after 3-4 weeks
- **Anti-Cholinergic (Anti-Muscarinic= Atropine-Like).**
  - Amitriptyline > Imipramine > Desipramine.
- **Anti-Histaminic (H1-Block).**
  - Sedation & Hypnotic effect (↓ REM): doxepin > Amitriptyline > Desipramine.
- **Anti-Serotonin**
- **α1 blocking effect** → Postural hypotension, tachycardia, cardiac arrhythmias

Antidepressant drugs

❖ Therapeutic uses

1- Antidepressant drugs
2- Panic & phobic disorders.
3- Obsessive compulsive disorders (Clomipramine or Fluoxetine).
4- Prophylaxis of migraine: Amitriptyline is effective
4-Chronic pain as neuropathic pain (± Phenothiazine major tranquilizer). .
5-Treatement of nocturnal enuresis (replaced by desmopressin)

❖ Side effects:

- **Atropine-like' side effects**: Dryness of mouth, blurring of vision, constipation, urinary retention, etc.
- **α1 adrenergic blocking effects**: Postural hypotension, tachycardia, cardiac arrhythmias,etc.
- **H1-blocking effects**: Sedation and confusion.
- **Other effects:** Increased appetite, weight gain; convulsions may be precipitated.

❖ Contraindications:

- Prostatic hyperplasia. - Glaucoma.
- Epilepsy. - Cardiac arrhythmia

❖ Drug interactions:

- They displace other highly protein bound drugs eg phenytoin, warfarin .
- Severe CNS excitation occur if tricyclic antidepressants with MAO inhibitors.

Antidepressant drugs

2. Selective Serotonin Reuptake Inhibitors: (SSRIs)

Preparation:

- Fluoxetine
- Citalopram
- Sertraline (Zoloft)®
- Paroxetine
- Escitalopram
- Fluvoxamine

❖ Mechanism of action

- Inhibit neuronal reuptake of 5-HT selectively → ↑ synaptic serotonin concentration → **Antidepressant action, Appetite suppressant, Sexual dysfunction**
- Onset of action 2-3 Weeks →Down-regulation of 5-HT 2 receptors resulting from the prolonged increase in synaptic serotonin concentration.
- little or no effect on noradrenaline reuptake
- First choice drugs replaced TCAs and MAO inhibitors → less toxicity.

- **Advantages**
  - **Less Adverse Effects** → NO Anticholinergic (Allowed in Glaucoma patients) or CVS side effects or weight gain. No hypotension • No sedation • Do not precipitate convulsions
  - Low acute toxicity → No Cardiotoxicity or Hepatotoxicity
  - Little interactions & NO Interaction with food.
  - Long acting due to formation of active metabolites .They are administrated once daily.

Antidepressant drugs

Pharmacokinetics

- Given orally (once daily) with delayed onset of action. Food has little effect on absorption (except with sertraline, for which food increases its absorption
- Metabolism by CYP450 –dependent enzymes and glucuronide or sulfate conjugation
- Fluoxetine and paroxetine are potent MHE inhibitor →decrease metabolism & increase activity of co-administrated drugs

❖ Therapeutic uses:

- Depression. (they have similar efficacy to tricyclics, but are much more expensive)
- Obsessive-compulsive disorders. Fluvoxamine
- Generalized anxiety and panic disorders. Citalopram & Paroxetine
- Treatment of bulimia (excessive eating). Fluoxetine

❖ Side Effects:

- GI symptoms like nausea, vomiting and diarrhoea
- Sexual dysfunction. (decrease libido and delayed ejaculation)
- Insomnia, and agitation
- SSRI Withdrawal syndrome → headache, agitation and sleep disturbances.

- SSRIs + MAOIs or TCAs → serotonin syndrome (hyperthermia, muscle rigidity, tremors and mental confusion)

3. Serotonin and noradrenaline reuptake inhibitors (SNRIs)

Preparation: duloxetine, venlafaxine

- Inhibit the reuptake of serotonin and noradrenaline into the neuron
- Venlafaxine has less affinity for the NE transporter than duloxetine.
- The SNRIs differ from the TCAs in lacking significant blocking effects on peripheral receptors; ie, they do not block histamine H1, muscarinic, or α-adrenergic receptors.
- Orally effective
- May be effective in treating depression in patients in whom SSRIs are ineffective
- May be effective in treating depression is often accompanied by chronic painful symptoms
- **Side Effects**: Nausea, sweating, sexual dysfunction, hypertension

4. MAO inhibitors:

- **Monoamine oxidase (MAO)** is a mitochondrial enzyme involved in the metabolism of biogenic amines.

- There are two types of MAO enzyme:
  - MAO-A metabolizes NE, 5-HT and dopamine.
  - MAO-B metabolizes dopamine.

Preparation:

- **Non-selective (block MAO-A & MAO-B)** (irreversible): phenelzine & tranylcypromine.
- **Selective MAO-A inhibitors** (Reversible): meclobamide.
- **Selective MAO-B inhibitors**: selegiline (used in parkinsonism)

Mechanism of action:

- They block the action of MAO enzyme → ↑ concentration of monoamines in neuron.

- Selective MAO-A inhibitors have less side effects than Non-selectives.
- Used in depression and phobic disorder (unresponsive or allergic to TCAs and SSRIs).
- Delayed onset of action. (2-3 weeks)

Antidepressant drugs

❖ Side effects:

- ➢ Delayed onset of action. (2-3 weeks)
- ➢ Dry mouth, constipation& blurred vision (atropine-like action)
- ➢ CNS stimulation: agitation, insomnia, tremors& delirium.
- ➢ Hepatotoxic.

❖ **Drug-food interaction:**

- Foods containing tyramine as aged cheese, yogurt or broad beans + MAO inhibitors → hypertensive crises.
- Tyramine (degraded by MAO) → ↑ release of stored NE → hypertension, cardiac arrhythmia and stroke.
- This reaction was treated by phentolamine, prazosin or Na nitroprusside.

❖ **drug drug interactions:**

- ➢ They augment the hypertensive effect of direct sympathomimetics eg adrenaline, dopamine ,
- ➢ It causes serotonin syndrome (hyperthermia , flushing , hypotension) if combined with serotonin reuptake inhibitors.
- ➢ It causes severe CNS stimulation and convulsions if combined with tricyclic antidepressants

Antidepressant drugs

5. Atypical antidepressants:

Preparation: bupropion, mirtazapine, nefazodone , trazodone, vilazodone.

1. Bupropion

- Inhibits the reuptake of dopamine and NA into the neuron
- Useful for major depression, smoking cessation
- **Side Effects**: Dry mouth, tremor, sweating, convulsions

2. Mirtazapine

- Increases NA and 5-HT release by antagonist at presynaptic α2 receptors
- It is an antagonist at histamine H1 receptors and 5-HT2 & 5-HT3 receptors but no anticholinergic
- **Side Effects:** Sedation, weight gain

3. Trazodone, nefazodone

- Inhibition of 5-HT2A receptor
- It is an antagonist at histamine H1 receptors but no anticholinergic
- **Useful f**or Major depression, sedation and hypnosis (trazodone)
- **Side Effects:** Sedation

Antidepressant drugs

The effects of antidepressants on receptors

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	+	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertraline	0	0	0	0	0	+++
Trazodone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++
Vortioxetine[1]	ND	ND	ND	ND	+	+++

[1] Vortioxetine is an agonist or partial agonist at 5-HT_{1A} and 5-HT_{1B} receptors, an antagonist at 5-HT_3 and 5-HT_7 receptors, and an inhibitor of SERT.

ACh M, acetylcholine muscarinic receptor; α_1, alpha$_1$-adrenoceptor; H_1, histamine$_1$ receptor; 5-HT_2, serotonin 5-HT_2 receptor; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

Treatment of mania and bipolar disorders (mood stabilizer) :

- Drugs used in bipolar disorder are lithium, carbamazepine, sodium valproate, olanzapine, risperidone, haloperidol, etc.

1. Lithium

- Antimanic & Mood Stabilizing agent.
- Used mainly as mood stabilizing in Bipolar affective disorder.
- Not very effective in acute mania → Weak & Slow onset.

❖ Mechanism of action:

- Lithium decreases the release of NA and DA in the brain → Antimanic .
- Increases 5HT actions in the CNS. 5HT1A agonist and 5HT2 antagonist. → antidepressant activity
- Lithium also inhibits the activation of adenylate cyclase enzyme induced by hormones (ADH & Thyrotropine) and neurotransmitters (NE).

Treatment of mania and bipolar disorders (mood stabilizer)

❖ Pharmacokinetics

- Lithium is given as a salt (e.g. carbonate, citrate), which is rapidly absorbed from the gut
- Distributed in total body. NOT bound to plasma proteins.
- NO Hepatic Metabolism.
- Excreted in urine & other body fluids (Tears, Saliva, Sweat & Milk).
- stopped gradually. - Has low therapeutic index.

❖ Therapeutic Uses of lithium

- Prophylaxis and treatment Bipolar affective disorder. (NB: Other drugs e.g. Carbamazepine & Lamotrigine).
- Treatment of depression and mania
- Treatment of inappropriate (increase) secretion of antidiuretic hormone.

❖ Side effects:

- Ataxia, confusion, Anorexia, nausea & vomiting.
- ↓ ADH → Polyuria & polydipsia (diabetes insipidus)
- Hypothyroidism.
- Renal failure.
- Teratogenic effect.

Treatment of mania and bipolar disorders (mood stabilizer)

❖ Drug interactions:

- Thiazide diuretics → deplete Na+ → ↑ serum Li+ level.
- NSAIDs → ↓ Li+ excretion → ↑ serum Li+ level.

NB: Li+ may be given in combination with anxiolytics (benzodiazepines), antiepileptics (carbamazepine) and antipsychotics (haloperidol) in treating mania.

Treatment of mania and bipolar disorders (mood stabilizer)

Other Drugs Used in Mania and Bipolar Disorder

- **Sodium valproate**: It is the preferred drug for the treatment of acute mania because of its rapid action, wider therapeutic index and better tolerability than lithium. It is useful prophylactically for bipolar disorder.

- **Carbamazepine**:, an antiepileptic drug, has mood-stabilizing effect and is used in the treatment of bipolar disorder. It may be used alone or in combination with lithium or valproate. It is used prophylactically in bipolar disorder.

- **Atypical antipsychotics**: Olanzapine, risperidone, aripiprazole, quetiapine, etc. are preferred agents to control acute attack of mania.

- **Benzodiazepines** like lorazepam or clonazepam are used as adjuncts if patient is agitated.

Treatment of mania and bipolar disorders (mood stabilizer)

Drugs of choice in treatment of affective disorders:

1-Mild and moderate depression , start with serotonin reuptake inhibitors (fluoxetine) →
No response after2-3 weeks
Add desipramine or bupropion → give another antidepressant drug group.

2-Depression in agitated patient → → give sedative antidepressant drugs eg doxepin & trazadone & maprotiline or secondary amine tricyclic antidepressant drugs

3- Depression with socially withdrawal or sedation → →Give the least sedative drugs eg bupropion & &protriptyline or tertiary amine tricyclic antidepressant drugs.

4- Atypical & depression & Phobic states → → MAO inhibitors.

5-Bipolar mood disorder → → give lithium carbonate or antipsychotic drugs (clozapine) or carbamazepine.

6-Mania give lithium carbonate

Antipsychotics

Antipsychotics

Major tranquillizers = Neuroleptics = Antipsychotics

- Antipsychotics are drugs used to control manifestations of psychosis e.g. Schizophrenia

- **Psychosis** (Schizophrenia): disorder in thoughts, behavior, and emotions characterized by:
  - Positive symptoms: as hallucinations (usually auditory) and delusions.
  - Negative symptoms: emotional dullness (emotional blunting), dementia, and social withdrawal (poor socialization).

- Psychosis may be due to
  - ↑ activity of dopamine-stimulating D2-receptors.
  - 5HT has a modulatory effect on dopamine pathways Many effective antipsychotic drugs have dopamine and 5HT2 receptor-blocking properties.

❖ Antipsychotic drugs (neuroleptics or major tranquillizers)

- Inhibition of D2 dopaminergic receptors and/or 5HT2 serotonergic receptors.

- Their side effects are due to blockade of muscarinic M1 ,M3 receptors , histamine H1 receptors , α1 receptors , sodium and potassium channels and hypersensitivity reactions

- They are classified into:
  - **Typical agents:** have a high DA to 5HT blocking ratio (more effective against +ve symptoms)
  - **Atypical agents:** have a high 5-HT2 to D2 blocking (more effective against –ve symptoms)

Antipsychotics:

1- First generation antipsychotics (Typical neuroleptics)

- Act by blocking of dopamine D2 receptors leading to ↓ hallucinations and delusions
- Have extrapyramidal side effects.(EPS)

I. Low potency:

1- **Phenothiazines:**

- chlorpromazine → α1 = 5-HT2A > D2 > M = H1 blocker, **weak** Antipsychotic & antiemetic , high EPS. High sedation and weight gain (5HT2 blockade), high Cardiovascular side effect (α 1& Na channel blockade), Hypersensitivity reaction: hepatitis

- Thioridazine → similar to chlorpromazine, α1 > D2 = M, Less 5HT 2& H1 receptors : weak antipsychotic & antiemetic, Mild or no ESP (inhibits D2 = M). Mild sedation, high Cardiovascular side effect (α 1& K channel blockade), Corneal and retinal deposits

.

II. High potency: More EPS, less H1, α1 and M blocking effect.

1- **Phenothiazines**

- Trifluoperazine, Fluphenazine→ similar to chlorpromazine, BUT: More D2-Block, less H1, α1 and M blocking effect → More Powerful Anti-psychotic & antiemetic, More EPS .

Antipsychotics:

2- Butyrophenones

- Haloperidol, droperidol, → Block more D2 > 5HT2, less H1, α1 and M receptors, Stronger → Antipsychotic, Anti-Emetic & EPS. Moderate sedation & weight gain (5HT2 blockade), Mild or no cardiovascular side effects

3- Thiothixene,. Flupenthixol Zuclopenthixol- → Block more D2 = 5HT2 > α1, less H1, and M, → **high antipsychotic potency**, more EPS & Moderate postural hypotension, less sedative.

2- **Second generation antipsychotics**: (Atypical neuroleptics)

- Act by blocking of both 5-HT2 receptors and D2 receptors in limbic.
- Have fewer EPS, and have a little effect on muscarinic, histaminic and α-receptors
- Second-generation agents are generally used as first-line therapy for schizophrenia.

- Clozapine –→ Block more M = 5HT2 = D4 > H1= α1 >D2 receptors, → Antipsychotic effect, Moderate sedation, No EPS. Moderate postural hypotension, Agranulocytosis, high weight gain.
- Olanzapine → Similar to clozapine with no agranulocytosis.
- Risperidone - → 5HT2 > D2 receptors, **High Antipsychotic potency**
- Pimozide and Sulpiride → Block D2 selectively, no effect 5HT2.
- Aripiprazole (partial agonist D2 and 5-HT1A receptors, antagonist of 5-HT2A receptors. → Antipsychotic, No anti-Emetic & EPS. less weight gain (preferred in obese patients).

Antipsychotics:

❖ Therapeutic uses of typical antipsychotic drugs

- **Schizophrenia – antipsychotic drugs**. The antipsychotic effect starts after few hours and reach maximum after 2-4 weeks of continuous treatment.
  - Risperidone, olanzapine and haloperidol are frequently used.
  - Clozapine is reserved for resistant cases of schizophrenia.
  - **NB:** typical antipsychotic more effect on positive symptoms, while atypical drugs more effect on negative symptoms.
  - Risperidone & aripiprazole are now approved for the management of the disruptive behavior & irritability secondary to autism.

- **Treatment of mania with bipolar disorder**:

- **Anti-emetic** in small doses. (not used in motion sickness or pregnancy) (chlorpromazine and promethazine)

- Premedication and (to reduce anxiety and inhibit vomiting). (Chlorpromazine)

- In neurolept-analgesia: Droperidol + Fentanyl (Opioid Analgesic) → for minor operations. The emetic effect of Fentanyl is Antagonized by the Antiemetic effect of Droperidol

- **Anti-pruritic** in treatment of itching.

❖ Side effects

1. Extrapyramidal manifestations:
- In therapeutic dose: parkinsonian like symptoms
- In large dose or long acting preparations or potent drugs: **Malignant neuroleptic syndrome** (severe muscle rigidity , hyperthermia , fluctuation of blood pressure , mental confusion. It is treated by dantrolene (skeletal muscle relaxant)
- Tardive dyskinesia (Abnormal movement, late, after 2-5 years) due to up regulation and super sensitivity of D_2 receptors in basal ganglia. It is treated by benzodiazepines which decrease dopamine release.

2. **Anti-muscarinic effects:** Dry mouth, blurred vision, constipation and urinary retention.
3. **Postural hypotension** and reflux tachycardia.
4. **Sedative action**
5. **Gynecomastia** , loss of libido in males .Infertility in females due to increase of prolactin secretion as a result of D2 receptor blockade
6. **Weight gain:** due to 5HT2 blockade
8. **Hypersensitivity reactions: jaundice (e.g. chlorpromazine)**
9. Non dangerous corneal or retinal opacities more commonly with thioridazine
10. **Agranulocytosis**. (clozapine)
11. **Induction of seizures**. (chlorpromazine and clozapine)

Antipsychotics:

❖ Contraindications

- Allergy and liver diseases
- Parkinsonism
- Epilepsy.
- Pregnancy.
- Glaucoma and enlarged prostate.
- Hypotension.

❖ Drug interactions:

- Antipsychotics → ↑ sedative effect of alcohol, barbiturates and BDZs.
- Antipsychotic → ↓ action of adrenaline.

Antiseizure (Antiepileptic) drug

Antiseizure (Antiepileptic) drug

❖ **Epilepsy**.

- Chronic disease characterized by repeated attacks (seizure) of abnormal electrical discharge of cerebral neurons → motor, sensory, autonomic or psychological changes

- **Causes of epilepsy**:

  - Primary epilepsy: may be due to long term excitation (glutamate release)
  - Secondary epilepsy caused by: Trauma, meningitis, brain tumors, fevers, hypoglycemia. Some drugs: insulin (hypoglycemia) – TCAs - cocaine- Li+.

❖ **Types of epilepsy:**

A. Partial (focal) seizures: Focal seizures (one lobe of one hemisphere)

1. **Simple partial**
   - No loss of consciousness, Clonic jerking of single limb or a muscle group
   - May also show sensory disturbances.

2. **Complex partial**:
   - Complex sensory hallucinations, Motor dysfunction as chewing movement,
   - Some alteration or impairment of consciousness followed by amnesia of the attack

3. **Secondarily generalized convulsion (2ry generalized)**

- Partial seizure followed immediately by generalized (grand mal) attack due to spread of the discharge.

B. Generalized seizures:

1. **Tonic–clonic seizures (primary generalized, grand mal epilepsy):**
- Aura → loss of consciousness, → tonic (spasm) → clonic (shaking), → confusion & Fatigue and sleep.

2. **Absence (Petit mal**), **non convulsive epilepsy**:.
- Sudden brief (l0-l5seconds) loss of consciousness usually without motor disturbances. It starts at the age of 2-12 years and either stop at the age of 20 or develop into grand mal..

3. **Myoclonic**
- Short jerking of a limb or the whole body without loss of consciousness

❖ **Status epilepticus**
- **A**n emergency due to severe sustained seizures without the recovery of consciousness in between or a single episode lasts longer than 30 minutes → brain damage or may be fatal.
- It is commonly due to sudden withdrawal of antiepileptic drugs**.**

❖ Mechanism of action of antiepileptic drugs:

- Anti-epileptics block initiation or spread of seizures by:
  - ↓ hyper-excitability of cerebral neurons by acting on neurotransmitters
  - blocking ion channels.
- Most antiepileptic drugs act by more than one mechanism:

➢ **Block Na+ channel**: in Partial & Grand Mal epilepsy (e.g. phenytoin, carbamazepine, Valproate, lamotrigine, lacosamide , rufinamide, topiramate, felbamate, zonisamide)

➢ **Block T-type Ca+2 channel :** used in Petit mal epilepsy(e.g. ethosuximide &Valproate)

➢ **GABA augmenting agents** (e.g. benzodiazepines, barbiturates and Valproate)
- phenobarbital & BZD are used mainly in acute siezure & in status epilepticus. Due to sedation & tolerance.
- Phenobarbital (in tonic-clonic & partial) & clonazepam (in Petit mal & myoclonic) are used as 2nd line or adjuncts to other agents.

➢ **Decrease the excitatory effect of glutamates**,
- Glutamate receptor blockers (e.g. topiramate, felbamate, lamotrigine, Valproate)

➢ **Synaptic vesicle protein 2 binders** (e.g. levetiracetam)

A- Sodium channel blockers

1. **Phenytoin** (Diphenylhydantoin oral or i.v) & Fosphenytoin i.v, i.m. form

❖ Pharmacokinetics

- Orally: Irritant (Used after meals) for seizure prophylaxis, Slow i.v. in Status epilepticus.
- Passes BBB. - Passes placental barrier (teratogenicity) – Highly bound to plasma proteins
- Metabolized by H M E → ↑enzyme induction and increases the rate of metabolism of co-administered drug) → Tolerance & ↓ the effects of co-administrated drugs .

❖ Mechanism of action

- Block Na+ channel in brain and heart → Delay recovery → ↓ Rate of firing → Membrane stabilization. → prevents or reduces the spread of seizure discharges
- **Action on CNS:** Antiepileptic, analgesic, Non sedative
- In cerebellum and vestibular system: ataxia, Vertigo and nystagmus
- **Peripheral actions:** Antiarrhythmic , Decrease ADH

❖ Therapeutic uses:

- **Treatment of epilepsy**: in partial (focal), Generalized tonic–clonic seizures (grand mal) and Status Epilepticus. Not used in petit mal epilepsy (may exacerbate seizures).
- **In ventricular arrhythmia** → Drug of Choice in Digitalis-Induced arrhythmia
- **Treatment of neuropathic pains as** trigeminal neuralgia

❖ Adverse effects

1. **GIT:** nausea & vomiting, gastric irritation (highly alkaline) → Used after meals.
2. **Blood:** megaloblastic anemia (↑ metabolism of folic acid and interfere with absorption of vitamin B12)
3. **Gingival (gum) hyperplasia especially in children.**
4. **Hypersensitivity reactions: rash, blood dyscrasias, and cholestatic hepatitis**
5. **Hirsutism and acne:** due to increased androgen secretion,. It is therefore usual to avoid phenytoin in young women or adolescents.

6. Cerebella-Vestibular manifestations (At high concentrations):-ataxia- Vertigo -nystagmus.

8. Inhibits ADH and insulin release (may cause hyperglycemia).

9. Osteoporosis due to increase vitamin D metabolism

10. Teratogenic (fetal hydantoin syndrome: cleft lip, cleft palate).

❖ Drug interactions:

- **Induction of cytochrome P450 enzymes** → tolerance & ↓ the effects of co-administrated drugs as: theophylline, cortisone, Barbiturates, Carbamazepine and oral contraceptives.
- **Other HME inducers** as barbiturates and carbamazepine → ↑ its metabolism.
- **HME inhibitors** as valproic acid → ↓ its metabolism → phenytoin toxicity.

Fosphenytoin

- It is a prodrug that is rapidly converted to phenytoin in the blood within minutes
- It is used in status epilepticus.
- It is available for i.m. and i.v. administration.
- It is less cardiotoxic when compared to phenytoin..

2. Carbamazepine: (Tegretol)®

- Acts by blocking of Na+ channels in the brain.
- It is structurally related to tricyclic antidepressants → Inhibit neuronal reuptake of NE →↑ concentration in brain → Mood Stabilizer in Bipolar manic-depression and ↑ADH release (water retention)

- **Action on CNS**: Antiepileptic, analgesic, mood stabilizer, non sedative
- In cerebellum and vestibular system: ataxia, vertigo and nystagmus

- Absorbed orally. Passes BBB. Passes placental. Metabolized by the liver.
- **HME Inducer** → ↓ effectiveness of the drug itself (tolerance) and other drugs as valproate, phenytoin, lamotrigine, topiramate, oral contraceptive.

❖ Therapeutic uses:

- **1st choice** in partial and 2nd choice in grand mal epilepsy. (not used in petit mal epilepsy)

- **Drug of choice in the treatment of trigeminal and other neuralgias (diabetic neuropathy)**

- **Treatment** of mania-depressive disorder (bipolar affective)

❖ Adverse effects

- Ataxia, diplopia, nystagmus, and vertigo & mild GIT irritation.
- **Hypersensitivity reactions**: rash, blood dyscrasias (aplastic anaemia and agranulocytosis), and cholestatic hepatitis
- **Fluid retention and hyponatremia** due to anti-diuretic action.
- **Teratogenic** (similar to fetal hydantoin syndrome).
- **Drug interactions** →↑ Metabolism of antiepileptics ,warfarin & other drugs

Carbamazepine derivatives: Oxcarbazepine, Esilacarbazine

- Related to carbamazepine. same mechanism of action and therapeutic uses, But less toxic & Less HME induction and more increase in antidiuretic (ADH) hormone.
- They are prodrug and is converted to active form responsible for its anticonvulsant activity
- **Oxcarbazepine** approved for use in adults and children with partial-onset seizures.
- **Esilacarbazine :** use similar to **Oxcarbazepine,** shown to be effective when given once daily
- **Side effect**: Similar to carbamazepine, but hyponatremia is more common; that limits its use in the elderly, unlike carbamazepine, does not induce drug metabolism

3. Valproic acid & Sodium valproate: (Depakine)®

- Block Na+- & Ca2+ -Channels → Effective in Partial & Grand Mal & Absence seizures
- ↓ GABA-transaminase enzyme → ↑ GABA and NMDA receptor blockers → ↓ the excitatory effect of glutamates
- Absorbed orally. - Passes BBB. - Passes placental barrier - Highly bound to plasma proteins and displaces other drugs as phenytoin. - Metabolized by the liver.
- EHM inhibitor → ↓ metabolism of co-administrated antiepileptic drug

❖ **Therapeutic uses**: less sedating, a broad-spectrum antiepileptic drug. All types of epilepsy

- 1st choice in:
  - Grand mal, Petit mal, and Myoclonic epilepsy
  - Mixed petit mal + grand mal. (preferred to ethosuximide)
- 2nd choice in Partial seizures
- Treatment of mania, Mood stabilizer in Bipolar disorders and prophylactic migraine

❖ **Side effects:**

- Nausea, vomiting, drowsiness, and Weight gain
- Hepatotoxicity & Teratogenicity & pancreatitis due to Free radical formation
- HME inhibitor. → ↓ metabolism → ↑ effect & toxicity of co-administrated drugs as (phenytoin, carbamazepine, lamotrigine)

4. Lamotrigine:

- Block Na+ & calcium channels and inhibit glutamate release
- Well absorption , long half life , low protein binding , no effect on HME, non-sedatives
- It has a broad spectrum of antiepileptic activity.
- Used as a monotherapy or ad- on for all types of epilepsy (partial and generalized seizures, absence, myoclonic seizure).
- Also in bipolar disorder – Analgesic in neuropathic pain
- Less teratogenic can be used in small doses during pregnancy

❖ **Adverse effects:** hypersensitivity reaction skin rash (Stevens-Johnson syndrome) , dermatitis - ataxia,

- **Drug interactions**: Valproic acid → ↓ metabolism of Lamotrigine and dose adjustment. Lamotrigine dosages should be reduced when adding valproate to therapy

5. Zonisamide

- It is a sulfonamide derivative, weak (add on).
- Block Na+ & calcium channels and inhibition of carbonic anhydrase enzyme
- It is used as adjuvant in combination with other drugs in Generalized tonic-clonic, partial, and myoclonic seizures.
- **Adverse effects:** drowsiness, skin rash, weight loss, kidney stones

5. **Lacosamide & Rufinamide**

- Block Na+ channels, It is more safe , less active.
- It is used as adjuvant (add on) drug in resistant cases.
- Not used alone or in acute epilepsy

B-Block T-type Ca+2 channel: used in non convulsive petit mal epilepsy

e.g.: Ethosuximide (Succinimide)

- Acts by blocking T-type calcium channels.
- It has rapid and prolonged effect and complete GIT absorption , low plasma protein binding , no effect on microsomal enzymes , no active metabolites , renal excretion).
- Used in non convulsive epilepsy (petit mal epilepsy).
- Ethosuximide and valproate are the drugs of choice for absence seizures and are more effective than lamotrigine.

❖ **Side effects (safest):** GIT upset, skin rash, dizziness, drowsiness, headache.

C- Drugs that augment GABA action

- (benzodiazepines and barbiturates)
  - **Barbiturate receptor agonists**: Phenobarbitone , primidone
  - **increase GABA release**: Gabapentin & pregabalin
  - **inhibits GABA metabolism**: Vigabatrin
  - **inhibits GABA reuptake**: Tiagabine

- All GABA augmenting agents have sedative, anti-anxiety, skeletal muscle relaxant effects and produce weight gain.
- All of them has analgesic effect used in treatment of neurologic pain except barbiturates.
- Contraindicated in non convulsive epilepsy except benzodiazepines .

1. **Barbiturate**: Phenobarbitone & primidone (a prodrug converted to phenobarbitone, more effective than Phenobarbitone)

- Acts by enhancement of GABA-mediated, inhibition of glutamate excitation.
- Long half-life, HME inducer, sedative, tolerance
- Potent but very toxic.
- **Therapeutic uses**: 2nd line in grand mal epilepsy and partial seizures (contraindicated in petit mal epilepsy).
- Phenobarbitone is used in the treatment of status epilepticus (when the convulsions are not controlled with diazepam and phenytoin).

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للتواصل معنا:

https://t.me/MohammedMarwan

967775181417+

2. **Benzodiazepines:** Diazepam, lorazepam & Clonazepam

- Diazepam, lorazepam &Clonazepam are the drugs of choice in status epilepticus. (slowly IV)
- Lorazepam: more effective and longer acting than diazepam in the treatment of status epilepticus, hence preferred in status epilepticus.
- Clonazepam, a long-acting benzodiazepine, is used orally in absence and myoclonic seizures.

3. Vigabatrin:

- Irreversible inhibitor of GABA transaminase enzyme (the enzyme responsible for metabolism of GABA).
- Vigabatrin is used only in combination with other drugs to treat epilepsy that is resistant to other drug combinations
- Used in infantile spasm and partial seizures refractory to other treatments.
- **Side effects:** sedation drowsiness, depression, blurred vision, Weight gain

4. **Tiagabine**:

- Blocks GABA uptake into presynaptic neuron.
- Used as adjunctive treatment in partial-onset seizures refractory to other treatments.
- **side effects**: sedation, dizziness and GIT disturbances.

5. **Gabapentin & Pregabalin** :

- Analog of GABA (↑ GABA release).
- Used as adjunctive to partial and grand mal epilepsy.
- Used also in diabetic neuropathic pain.
- **Side effects**: Sedation , dizziness and ataxia, Weight gain from stimulation of appetite. .

D- Glutamate inhibitory drugs

- All of them are weak , adjuvant (add on) drugs. They are not used alone .
- They are used in combination with other drugs in resistant cases of all types of epilepsy
- They are used in treatment of mania , bipolar depression and migraine

1. Topiramate

- It has a broad spectrum of antiepileptic activity
- Blocks glutamate receptors and block voltage-dependent Ca2+& Na+ channels and potentiates GABA by binding GABA receptors. a carbonic anhydrase inhibitor
- It is used in partial, generalized seizures, absence, myoclonic, Lennox-Gastaut syndrome. prophylaxis of migraine

❖ **Side effects**: weight loss, and. Renal stones, glaucoma

2. Felbamate:

- Has a broad spectrum of anticonvulsant action with multiple mechanisms including: blocking Na+& Ca+2 channels and glutamate receptors and also potentiates GABA.
- It is highly toxic causes aplastic anemia and severe hepatitis.
- It is reserved as third-line drug for refractory cases.

E- Drugs that modulate the action of synaptic vesicle protein 2 (SV2A)

- Levetiracetam

- Broad spectrum, non sedating, not metabolized by cytochrome P450, add on (adjuvant) drugs used in combination with other drugs
- It is approved for adjunct therapy of focal onset, myoclonic, and generalized tonic–clonic seizures in adults and children.

❖ **Side effects:** dizziness, ataxia, insomnia and weight loss.

❑ They are relatively safe during pregnancy

Drugs used for treatment of Status epilepticus

1. 25% glucose and oxygen inhalation .If no response within 10 minutes give.
2. Benzodiazepines:
   - lorazepam i.v: 5 mg (0.1 mg/kg) or.
   - diazepam i.v.: 10 mg (0.2 mg/kg) or Rectal diazepam (10 mg rectal tube)

   Repeat the dose of benzodiazepine preparation. If no response within 10 minutes give

3. Fosphenytoin i.v. 15-20 mg/kg or Phenytoin i.v. 20 mg/kg infusion
   If no response within 10 minutes give

4. Phenobarbitone i.v.20 mg/kg + respiratory aids because diazepam and phenobarbitone are respiratory depressants. if no response within 10 minutes give

5. General anesthesia + respiratory aids + α receptor agonist if there is severe hypotension

Epilepsy in pregnancy:

- Avoid valproic acid, Na valproate, phenytoin and barbiturates.
- Give the drugs with the lowest doses.
- The pregnant women should be monitored regularly.
- Anti-epileptics (Phenytoin, phenobarbital, topiramate and carbamazepine) induce the metabolism of contraceptives pill → ↓ efficacy and unwanted pregnancy

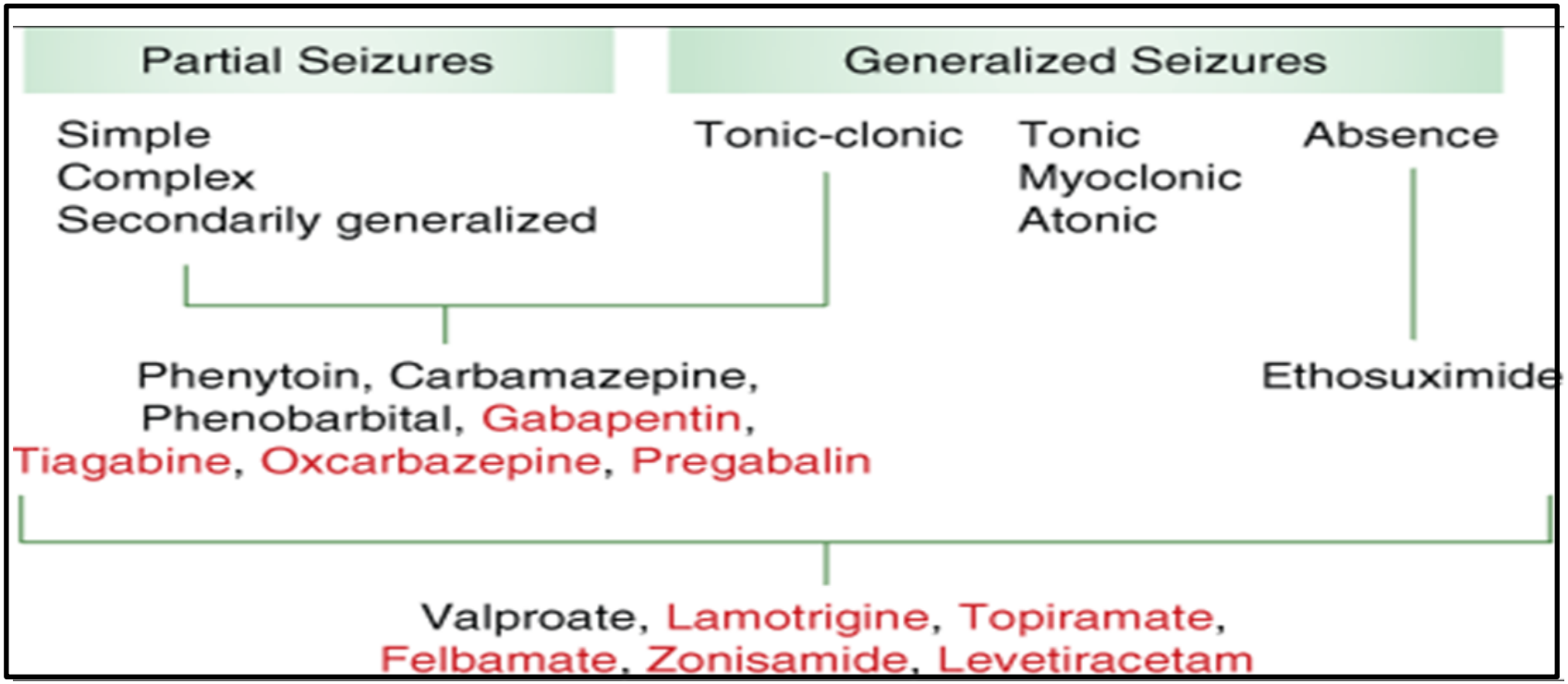
NB:

- Carbamazepine, phenobarbital, primidone and phenytoin induce HME (CYP450) → ↓ the plasma concentrations of several other antiepileptic drugs.

- valproate inhibits hepatic HME, → ↑ the plasma concentrations of some antiepileptic drugs

General principles in treatment of epilepsy

- Mono-drug therapy is advised to reduce adverse effects and drug interactions.
- Treatment should be continued for 2-3 years after the last seizure.
- Anti-Epileptics Drugs should be gradually withdrawn to avoid status epilepticus.



Choice of Antiepileptic Drugs in Different Types of Epilepsy

Seizure Type	Preferred Drugs	Alternative Drugs
Generalized tonic–clonic seizures (grand mal epilepsy)	Sodium valproate Lamotrigine	carbamazepine, Topiramate Primidone
Simple partial seizures (SPS)	Carbamazepine Sodium valproate	Gabapentin, Lamotrigine, Topiramate, Tiagabine, Levetiracetam, Zonisamide
Complex partial seizures (CPS)	Carbamazepine Sodium valproate Phenytoin	Gabapentin, Lamotrigine, Topiramate, Tiagabine, Levetiracetam, Zonisamide
Absence seizures (petit mal epilepsy)	Sodium valproate Ethosuximide	Clonazepam Lamotrigine
Myoclonic seizures	Sodium valproate	Clonazepam Lamotrigine Topiramate
Status epilepticus	Lorazepam Diazepam Fosphenytoin, Phenobarbitone	General anaesthetics—midazolam, propofol

Analgesics

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Narcotic Analgesics

Analgesics

- **Analgesics** are drugs that relieve pain without loss of consciousness

- **Classification of Analgesics:**

a- **Narcotic analgesics**: as Opioids
- ↓ Both pain and emotional response to pain (anxiety and fear).
- Used in moderate to severe pain.

b- **Non-narcotic analgesics**: as NSAIDs & Paracetamol
- ↓ pain sensation & No ↓ emotional response.
- Used in mild to moderate pain

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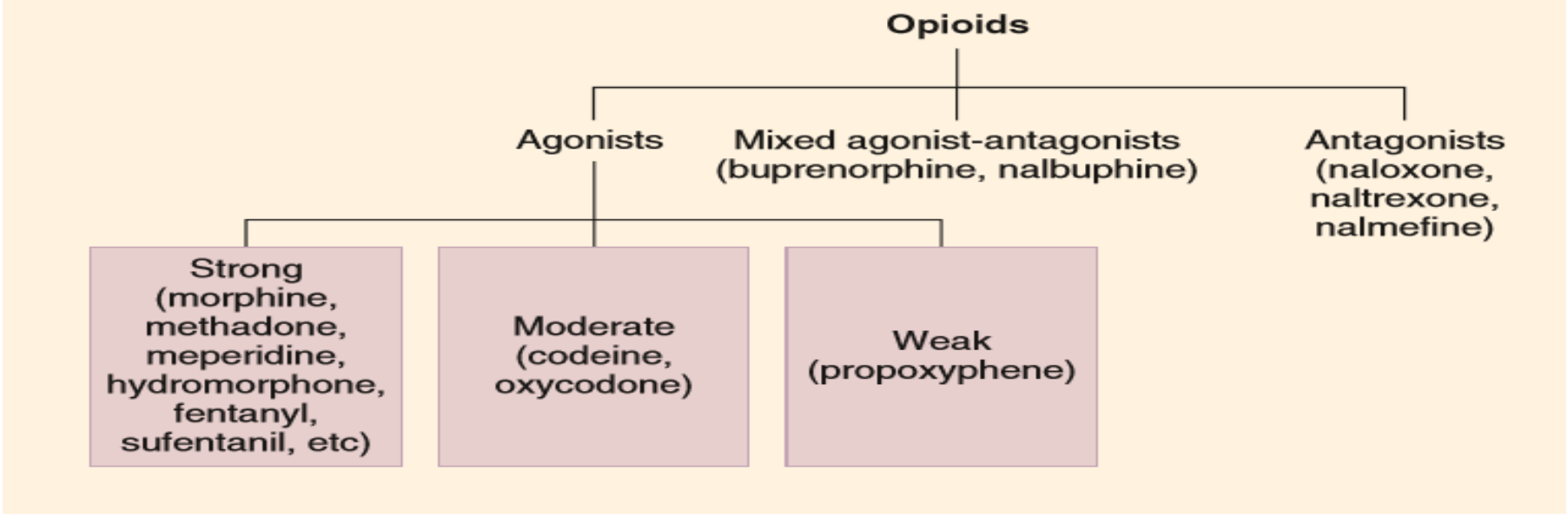
❖ **Narcotic analgesics: Opioids Analgesics**

- These are drugs that relieve the pain centrally
- Drug of choice in sever pain and malignant pain.
- In large dose they cause stupor & drowsiness
- On long use they produce tolerance & dependence.

❖ Narcotic analgesics: Opioids Analgesics:

❑ Sources

1. **Plant** (termed opiates, alkaloids; opium poppy)**:** morphine-codeine
2. **Semisynthetic opiates**: Heroin, hydromorphone, oxymorphone
3. **Synthetic**: fentanyl – methadone - pethidine.
4. **Endogenous (**termed opiopeptins)**:** endorphins-enkephalins- dynorphins released in the body ,acting on opioid receptors, producing morphine-like effects.



Classification of Opioids based on MOA

TABLE 28–2 ▪ Drug Actions At Mu and Kappa Receptors

Drugs	Receptor Type: Mu	Receptor Type: Kappa
Pure Opioid Agonists		
Morphine, codeine, meperidine, and other morphine-like drugs	Agonist	Agonist
Agonist-Antagonist Opioids		
Pentazocine, nalbuphine, butorphanol	Antagonist	Agonist
Buprenorphine	Partial agonist	Antagonist
Pure Opioid Antagonists		
Naloxone, naltrexone, nalmefene	Antagonist	Antagonist

❑ Opioid agonists

1. Morphine

- An alkaloid extracted from opium plant.
- Given orally but slow (bioavailability is 25%, extensive first-pass effect)
- Given also S.C., I.M. and I.V.
- Only a small of morphine crosses the BBB (least lipophilic of the opioids, while fentanyl & methadone are more fat soluble).
- Crosses placental barrier (Addiction of Fetus, Neonatal asphyxia During labor),
- Metabolized by conjugation → Morphine-6-glucuronide (more potent analgesic) & inactive metabolites.
- Excretion: renal (90%) – bile. Saliva, Breast milk

❖ Mechanism of action

- Act by stimulation of opioid receptors: Mu (mediate most effects of opioids) and κ-receptors present in the CNS and periphery (e.g.GIT).

Analgesics

❖ Pharmacological actions:

❑ On CNS:

- **Inhibition** : Sensory area (Analgesia), Cough center (central antitussive action), Respiratory center (CO2 retention and cerebral VD → ↑↑ intracranial tension) and Vasomotor center (vasodilatation and hypotension).

- **Stimulation:** Sedation and euphoria, Miosis (pin-point pupil), CTZ (Nausea & vomiting)and Vagal center (bradycardia).
- **Physical and psychological dependence**: Repeated use of opioids causes physical and psychological dependence.

❑ On GIT & Urinary bladder:

- ↓ Intestinal peristalsis and ↑ the tone of the sphincters. → constipation & urinary retention .
- Construction of smooth muscle (Spasmogenic effects → GIT, urinary system, biliary system, and bronchi.

❑ ↑ **Histamine release** → itching, Bronchoconstriction and vasodilatation.

❑ Endocrine effects:

- ↑ Release of prolactin and growth hormone.
- ↑ Release of ADH (Antidiuretic Hormone) → urinary retention.

❖ Therapeutic uses:

1. Analgesic in severe pain (as cancer, fracture bones, MI, postoperative)

- In renal and biliary colic: Add Atropine in Biliary & Renal colic.

2. Relief of cough. (dry cough): Codeine is more effective and has less side effects than morphine as antitussive.

3. Treatment of diarrhea: Diphenoxylate & loperamide (No addictive, more widely used as antidiarrhea.

4. Pre-anesthetic medication: because it reduces pain , anxiety and causes sedation of the patient .This may reduce the dose of anesthetic agent

5. **Treatment of acute pulmonary edema** (Acute left ventricular failure)→ ↓ both pre- and after-load (by vasodilatation).

❖ Adverse effects

- Nausea and vomiting, Constipation and increased biliary pressure, Urine retention.
- Bronchospasm and Itching (pruritus).
- Teratogenicity and Neonatal asphyxia during labor
- Bradycardia and Postural hypotension
- Tolerance and addiction =chronic toxicity.
- On sudden withdrawal symptoms may produced: severe pain , diarrhea , increase micturition, dysphoria ,anxiety , hypertension and increase respiration.

❖ Contraindications:

- Respiratory diseases. (as bronchial asthma or tuberculosis)
- Head injury. (↑ intracranial pressure) and Epilepsy
- Pregnancy, labor and lactation.
- Infants and elderly. due to deficient conjugation→ supersensitivity.
- Liver and kidney impairment.
- Undiagnosed acute abdominal pain
- Enlarged prostate
- Alone in biliary & renal colic.

❖ Treatment of morphine dependence

a. Hospitalization of the patient.
b. Gradual withdrawal of morphine.
c. Replace morphine with methadone which has long duration of action with less withdrawal symptoms
d. Gradual replace methadone with other sedative drugs which has less addictive potential eg benzodiazepines
d. opioid antagonist as naltrexone 300 mg once daily

❖ Acute overdose toxicity (acute morphine toxicity)

- Coma + pin point pupil due to severe miosis+ respiratory depression + hypotension+ Hypothermia

Treatment of acute morphine poisoning

- Positive pressure O2 therapy
- Morphine antagonists: naloxone 0.4 mg IV to be repeated every 10 minutes till complete recovery of respiration.

2. **Codeine** Natural Opium Alkaloid

- Similar to morphine with the following differences:
  - Has greater oral bioavailability (60%).
  - less potent analgesic (used only for mild to moderate pain) - less R.C. depression- less tolerance and addiction.
  - It is as potent as morphine as cough center depressant.

❖ **Therapeutic uses**

– Analgesic (10 mg) for mild to moderate pain (± Aspirin & Paracetamol).
– As central antitussive (15-30 mg at bed time) dry cough.

❖ **Adverse effects**: (less than morphine) – constipation and sedation.

3. Heroin

- They are semisynthetic opioids (heroin is diacetylmorphine).
- Rapid onset (greater lipid solubility → crosses BBB more than morphine
- They are more potent and more addictive than morphine.
- It is not used because it is highly addictive.

4. Meperidine: (Pethidine): orally, I.M injection

- Synthetic opioid. similar to morphine with the following differences:
  - It is very lipophilic, it has a rapid onset but shorter duration of action (3–4 h).
  - Has anticholinergic effects (atropine like effects).
    - No miosis may cause Mydriasis and central nervous system stimulation (convulsions).
    - Has spasmolytic action: they can be used in treatment of colics
    - less respiratory depression in neonates & does not delay labor→ preferred obstetric analgesia.
    - No antitussive effect. - Less constipating (shorter acting).
  - Agonist on mainly K receptors. less potent analgesic (1/10 as potent as morphine).
  - **Uses:** It is preferred to morphine in: 50-100 mg.
    - Renal and biliary colic (given alone because of atropine- like action)
    - Pain during labor (less or no R.C. depression of newborn).
    - Pre-anaesthetic medication (less R.C. depression-less emetic-less constipation).

- **side effects**
  - atropine-like actions → dry mouth, tachycardia, etc.
  - tremor, twitches and convulsions due to its metabolite, norpethidine → NOT used for more than 48 hours.
  - Tolerance and dependence: less than morphine

5. Fentanyl, Sufentanil, alfentanil, and remifentanil :

- Synthetic derivative of meperidine.
- High lipid solubility. Rapid onset and short duration of action
- Has anticholinergic effects (atropine like effects).
- Antihistamine effect → less bronchospasm, less itching
- Absorbed orally, given also by injection, transdermal patch. and intra-thecal
- Strong μ-Agonist → Strong Analgesic → 100 Times > Morphine
- **Used**

  - Analgesic in deep visceral pain, during labor and cancer pain
  - IV anesthesia (as analgesic and sedative effects):
  - To induce anesthesia. in cardiovascular surgery (safer).
  - Fentanyl + droperidol (major tranquilizer) → **Neurolept- analgesia**

Loperamide (Imodium)®, Diphenoxylate (+Atropine); (Lomotil) ®

- Derivatives of mepridine
- Morphine-like on G.I.T. → Constipation → Treat Diarrhea.
- Not pass B.B.B. → No C.N.S. actions.
- Large Dose of Diphenoxylate (Lomotil) especially in Children . → Narcosis (contraindicated in children)

❑ Methadone:

- Synthetic opioid similar to morphine with the following differences:
- The analgesic effect is equal to morphine. but less tolerance and addiction and much less severe withdrawal symptoms.
- Higher oral bioavailability and longer duration than morphine.
- The actions of methadone are mediated by μ receptors and antagonist of NMDA receptor and a norepinephrine and serotonin reuptake inhibitor → effect in neuropathic pain
- **Uses as:**

  - Analgesic in severe chronic pain(efficacy equal to morphine))

  -To control withdrawal of heroin & morphine, in treatment of addicts. (Gradual withdrawal of methadone is associated with less severe & Smoother withdrawal symptoms)

❑ Tramadol

- weak agonistic activity at μ-receptors. It also inhibits the reuptake of noradrenaline and 5-HT.
- Less constipation, respiratory depression & addiction than morphine.
- **Used** (oral, IM, TV): Analgesic in postoperative & chronic moderate pain & in neuropathic pain
- **Adverse effects**: It has relatively fewer side-effects than most opioids (but addiction can occur), It may induce seizures in epileptic patients.

❑ Mixed agonist-antagonists and partial agonists:

❖ Preparation:

- Pentazocine & nalbuphine & Butorphanol . (Agonist on K- receptors and weak antagonists on Mu receptors)
- Buprenorphine. (Partial Mu agonist and antagonist on K-receptors)

❖ Actions:

- Their action depends on previous exposure to opioids:
- In absence of morphine → Agonists → strong analgesics. (used parenterally in treatment of severe pain)
- In presence of morphine → Antagonists → produce withdrawal symptoms (pain , tachypnea , hypertension)..

❖ Clinical uses

1. Pentazocine & nalbuphine & Butorphanol used as Analgesics in deep visceral pain by stimulation of K-receptors. They have the following advantages: less addiction. ↑ Dose of these drugs → More Analgesia But No More ↓ R.C..

- Acts on K receptors → Dysphoria, hallucinations, (psychotomimetic effect)
- Pentazocine & butorphanol Causes sympathetic stimulation → tachycardia, palpitation, BP (contraindicated in patients with hypertension and ischaemic heart disease)

2. Buprenorphine (parenteral, sublingual):

- As an analgesic in postoperative pain, cancer pain and preanaesthetic medication , Weak addictive and weak withdrawal syndrome. - Help in treatment of morphine or heroin addiction

❑ Drug Interactions of Opioids

1. Opioids + other CNS depressants (sedatives, alcohol, antidepressants & antipsychotics) → additive CNS depression.
2. Pethidine + MAOIs → serotonin syndrome (hyperpyrexia- convulsions).
3. Partial agonist + pure agonist → withdrawal syndrome & ↓ analgesic effect.

❖ Opioid antagonists:

- Compete with morphine and other opioids on the opioid receptors.
- Rapidly reverse the action of agonists (R.C. dépression, constipation, miosis, vomiting).
- Used in the treatment of opiate toxicity and addiction.

1. Naloxone: IV & short -acting
- Pure antagonist.
- Short duration of action. (t1/2 = 1- 2 hours)
- Orally not effective because of high first-pass metabolism.

❖ **Therapeutic uses**: (antidote for opioid)

- Treatment of morphine and other opioid poisoning → 0.4 mg I.V. may be repeated.
- Opioid overdose , Opioid-induced Neonatal asphyxia.

2. Naltrexone: Oral & long-acting

- Similar to Naloxone → Pure antagonist, orally effective and has longer duration of action.
- **Uses**: 50 mg

- Maintenance therapy in addicts
- for opioid-blockade therapy to prevent relapse in opioid-dependent individuals.
- Treatment of alcoholism, as it reduces the urge to drink.
- Naltrexone can lead to hepatotoxicity.

Non narcotic analgesic

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Non-narcotic analgesics

1. Nonsteroidal anti-inflammatory drugs (NSAIDs).

- NSAIDs having anti-inflammatory, analgesic and antipyretic effect.
- Inhibition of COX enzyme → inhibition of prostaglandins (PGs) synthesis.
- All of the NSAIDs → reversible COX inhibitors, except aspirin → irreversible COX inhibitor.

❖ Actions:

➢ They block inflammatory prostaglandins:

- In the brain → analgesic action & antipyretic effect (↓ PGs in hypothalamus and ↑ heat loss through VD of skin vessels and sweating).
- In the site of inflammation → anti-inflammatory effect (↓ inflammatory mediators, vascular permeability and edema).

➢ They block physiological prostaglandins

- In platelets → antiplatelet action (aspirin in low dose) due to ↓ TXA2.
- In uterus → uterine relaxant (tocolytic action)
- In kidney →↓ Renal blood flow → Na+ and water retention and even nephropathy
- In stomach → peptic ulcers and bleeding.

Non-narcotic analgesics

❖ Classification of NSAIDs:

1. **Nonselective COX inhibitors:** inhibition of COX-1 and COX-2

a. **Salicylates**: Acetylsalicylic acid (Aspirin) & sodium salicylate: less effective, high side effects (peptic ulcer and hemorrhage) used mainly as antiplatelet

b. **Propionic acid derivatives**: Ibuprofen, ketoprofen, naproxen: rapid action , short duration , less side effects)

c. **Acetic acid derivatives**: Diclofenac (Voltaren)®, aceclofenac: good efficacy (stronger than ibuprofen) with relatively low incidence of side effects (more than ibuprofen but less than indomethacin).

d. **Fenamic acid derivatives**: Mefenamic acid: potent uterine relaxants and decrease uterine bleeding used in dysmenorrhea) .

e. **Oxicam derivatives**: Piroxicam, tenoxicam. (Prolonged duration , frequent cardiovascular side effects, Strong anti-inflammatory with ↑ risk of GIT bleeding.

g. **Indole derivatives**: Indomethacin: highly effective, high side effects.

Non-narcotic analgesics

2. **Preferential COX-2 inhibitors**:,e.g. meloxicam. (COXII specific in small dose but loss selectivity in large dose)

3. **Highly selective COX-2 inhibitors**: e.g. celecoxib, etoricoxib

- They act as analgesics, antipyretics, and anti-inflammatory with less side effects on GIT, or platelets..
- **Adverse effect:** coronary thrombosis (COX-2 is responsible for endothelial PGI2 synthesis), Skin rash with celecoxib (structurally related to sulfonamides). Nephrotoxicity (COX-2 is constitutive in kidney),

❖ Pharmacokinetic properties:

- Well absorbed orally, Highly bound to plasma proteins and displace other drugs
- Pass BBB, placental barrier and may cause teratogenicity is given in early pregnancy Hepatic metabolism
- Excreted in urine unchanged (as aspirin), some are partly excreted in bile and undergo enterohepatic recycle leading to long duration of action (as indomethacin and oxicams) → give once daily.

❖ Therapeutic uses of NSAIDs

1) **Analgesics:** in mild to moderate pain. (headache, toothache, dysmenorrhea) & cancer pain (added to opioids). Treatment of dysmenorrhea (mefenamic acid & ibuprofen &diclofenac. Salicylates not preferred → bleeding

2) **Antipyretics**: treatment of fever, paracetamol is preferred

3) **Anti-inflammatory** in rheumatoid arthritis, rheumatic fever and osteoarthritis

4) **Treatment of chronic gout**: .All NSAIDS are used in treatment of chronic gout except acetyl salicylic acid may cause gout due to competition of uric acid at the site of renal excretion

5) **As a prophylactic from thromboembolic** diseases (angina or MI).
- Aspirin taken in small doses for prophylaxis (75-150 mg /day) → selective irreversible inhibition of TXA2 synthetase → inhibition of platelet aggregation. (prolongs bleeding time)

6) **keratolytic agents:** Salicylates used locally (decrease thickness of skin) used in the treatment of hyperkeratotic skin lesions.
- Topical preparation is methyl salicylates in corns).

Non-narcotic analgesics

❖ Adverse effects (Effects Common to all NSAID:

1. **GIT**: Nausea, vomiting, ulceration and GI bleeding., which is minimized by taking:
   a. NSAIDs after food.
   b. proton pump inhibitors/H2-blockers/misoprostol with NSAIDs.

2. **Hypersensitivity reactions**: allergy, skin rash or bronchospasm.

3. **Chronic use of salicylates (salicylism**) → tinnitus, vomiting, hyperventilation & blurred vision.

4. **Reye's syndrome** → Use aspirin in children with viral infection → hepatic damage and encephalopathy. Hence, salicylates are contraindicated in children with viral infection.

5. **Teratogenic.** (premature closure of ductus arteriosus, delay labor and increase postpartum hemorrhage).

5. Idiosyncrasy (aspirin) → Hemolysis in patients with Favism.

6. Hypertension, NSAIDs may cause renal damage (Nephrotoxicity, less frequent with aspirin)

7. Increase bleeding tendency (stop aspirin 1 week before surgery).
   - large doses of aspirin inhibit activation of vitamin K leading to hypoprothrombinemia and bleeding.
8. Hyperuricemia (low-dose aspirin in gout)

❖ Contraindications:

- Bleeding disorders as hemophilia and purpura.
- Peptic ulcer.
- Bronchial asthma.
- Allergy.
- Idiosyncracy (Aspirin) in G6PD deficiency (Favism).
- Renal diseases.
- Hypertension. (after chronic administration)
- Pregnancy.
- Aspirin in children less than 12 years.
- Gout: (Aspirin)
- Before surgery: aspirin must be stopped at least 7 days before surgery.

❖ Drug interactions of NSAIDs

- Displacement of other drugs from plasma proteins e.g.: digitoxin, warfarin, and oral hypoglycemic drugs
- Antagonizes the antihypertensive action of B-blockers, thiazides, and ACE inhibitors
- $NaHCO_3$ in antacids decreases oral absorption of aspirin
- ↑ Risk of gastric ulceration with glucocorticoids

	Salicylates	Indole derivatives	Phenyl acetic acid derivatives	Propionic acid derivatives
Efficacy	Low	High	Moderate	Moderate
Speed and duration of action	Moderate speed & short duration	Moderate speed & intermediate duration	Moderate speed & intermediate duration	Rapid and short action
Specificity	Non specific COXI&II inhibitors	More inhibitor to COXI than COXII -Very potent antiinfalmmatory &uterine relaxant	Non specific COXI&II inhibitors - Very potent antiinfalmmatory	Non specific COXI&II inhibitors
Therapeutic uses	-Antiplatelets -Topical keratolytic -Inflammatory bowl diseases	-Precipitate labor -Patent ductus arteriosus -Severe soft tissue inflammations	-Analgesic in renal colic -Antiinflammatory In joint &soft tissue inflammations	-Acute pain -Dental pain -Headache -Antipyretic in children (does not cause Reye's syndrome
Toxicity	High	High	Moderate	Mild
More frequent side effects	-Hemorrhage -Peptic ulcer	-Renal impairment -Peptic ulcer - CNS disturbances: confusion, hallucinations, psychotic , seizures, and frontal headache	-Allergic skin rash -Gastrointestinal upset. -Headache	Less gastic upset and less bleeding tendency

	Salicylates	Indole derivatives	Phenyl acetic acid derivatives	Propionic acid derivatives
Drug interactions	-Displacement of oral hypoglycemic &oral anticoagulants from plasma protein sites	-Antagonism of diuretic & anti-hypertesive drugs	Mild antagonism of action of diuretics and anti-hypertensives & Mild protein displacement	The least drug interaction with diuretic & anti-hypertensive
Preparations	-Oral antiplatelet: acetyl salicylic acid -Topical : Methyl salicylates. -Oral antiinfammatory: Sodium salicylates & salicyl salicylates & buffered salicylates	-Indomethacin -Sulindac	aceclofenac -Diclofenac - A combination of diclofenac and misoprestol is available	Ibuprofen Ketoprofen -Naproxin

	Oxicam derivatives	Fenamic acid derivatives
Efficacy	High	Low
Speed and duration of action	-Slow action - Very long duration given once daily	Intermediate onset & short duration
Specificity	Non specific COXI&II inhibitors Strong anti-inflammatory	- Non specific COXI&II inhibitors - It has analgesic , antipyretic and weak antiinflammatory effect -Potent uterine relaxant
Therapeutic uses	-Chronic bone and joint inflammations	Dysmenorrhea -Antipyretic Anti-inflammatory
Toxicity	High	High
More frequent side effects	-Increased incidence of peptic ulcer and bleeding - Severe hypertension	-Hemolysis -Diarrhea -Hepatotoxicity
Drug interactions	Significant diuretic & anti-hypertensive	
Preparations	Piroxicam 40 mg/day -Tenoxicam 50 once daily	Mefenamic acid 250 mg/6 hours

2. Simple analgesics

Paracetamol (Acetaminophen): It is an analgesic, antipyretic with weak anti-inflammatory action.

- It acts by inhibition of PG centrally not in periphery
- It is well absorbed orally, pass BBB- pass placental barrier but not teratogenic.
- **Metabolism**: metabolized by the liver mainly by conjugation with glucuronic acid and sulphate. At high toxic dose convert into a hepatotoxic metabolite N-Acetyl –Benzoquinone → detoxified by glutathione in liver.
- **Excretion:** metabolites and unchanged paracetamol (about 5%) are excreted in urine.

- **Therapeutic dose** :It inhibits PG in brain → analgesic & antipyretic action.
- **Chronic large dose**: It inhibits COX I in the kidney →chronic renal failure (analgesic abuse nephritis).
- Acute large dose → produces oxidant which consume natural antioxidant (glutathione) → oxidative damage

❖ **Uses:** Therapeutic dose: 500 mg-1 g qid (orally or parenterally)

- **Analgesic** in superficial pains & **Antipyretic** in fever.
- In patients allergic to aspirin as in: Bronchial asthma- peptic ulcer- bleeding disorders- pregnancy, Gout, children with fever due to viral infections as influenza.

❖ Side effects:

- Minimal adverse effects.
- Chronic overdose may cause, hemolytic anemia and cardiac damage due to oxidative effect of the drug and chronic renal failure (analgesic abuse nephritis)
- Acute large dose cause acute hepatitis due to free radical formation (oxidative toxicity) and consumption of natural antioxidant (glutathione). It is treated by n-acetyl cystine or methionine which increase glutathione synthesis

❖ Acute paracetamol poisoning

- Acute overdosage occurs with toxic doses (10-15 g. in adults) due to saturation of conjugation pathway and formation of N-Acetyl –Benzoquinone which is not detoxified due to depletion of glutathione causes hepatotoxicity
- symptoms are nausea, vomiting, diarrhoea, abdominal pain, hypoglycaemia, hypotension, hypoprothrombinaemia, coma, etc. Death is usually due to hepatic necrosis.
- **Treatment**: mainly by SH donors as N-acetylcysteine used as antidote in acute toxicity within 6-8 hours. (Protects against hepatic necrosis).

Non-narcotic analgesics

❖ Selection of non steroidal anti-inflammatory drugs:

- The antiplatelet drug of choice is acetylsalicylic acid due to potent and irreversible inhibition of platelet thromboxane A2 .
- The antipyretic of choice in children is paracetamol due to little side effects.
- The non steroidal anti-inflammatory drug of choice in precipitate and premature labor is indomethacin due to its potent effect on uterine COX I.
- The non steroidal anti-inflammatory drug of choice in treatment of dysmenorrhea & menorrhagia mefenamic acid because it decrease blood loss during menstruation.
- The non steroidal anti-inflammatory drug of choice in chronic inflammatory diseases in joint and bones: Piroxicam due to potent and long action.

Anesthetics drugs

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General Anesthetics

General anesthesia

❖ General anesthesia:

- General anesthetics are drugs used in surgery to induce reversible loss of consciousness, analgesia, amnesia, skeletal muscle relaxation & inhibition of visceral reflexes

- There is no single anaesthetic agent that can produce all the above effects. Hence, the Balanced Anesthesia is used:

- **Balanced Anesthesia**: is used to achieve all requirements for general anesthesia & ↓ adverse effects of individual drugs, It includes:

1. **Pre-anesthetic medications:** preoperative administration of sedatives, opioid analgesics, anti-muscarinics, anti-emetics and H2 antagonists aiming to:
   a. reduce anxiety and produce amnesia & facilitating induction of anesthesia.
   b. Suppress autonomic reflexes, ↓ salivary & bronchial secretion, ↓ gastric acidity.
   c. Potentiate weak anesthetics.

2. **Induction of anaesthesia** (i.v. anaesthetics e.g. propofol). + succinylcholine (for intubation).

3. **Maintenance of anaesthesia** (inhalation anaesthetics e.g. isoflurane/halothane). & neuromuscular blocker (if needed) in operation

General anesthesia

❖ Stages of General anesthesia

❑ **Stage 1**: Induction, Analgesia.
- Patient is conscious, loss of pain sensation and amnesia.

Stage 2: Excitement and delirium
- Patient loses consciousness, →↑ Sympathetic activity; ↑ Heart rate, ↑ blood pressure; and respiration. Vomiting may occur

Stage 3: Surgical anesthesia. (Desirable stage)
- Patient is unconscious with normal respiration, BP and size of pupil.
- No movement or pain reflexes.

Stage 4: Medullary paralysis.
- ↓ Vital Medullary Centers: respiratory and cardiovascular failure → death
- Ventilation and/or circulation must be supported to prevent death.

❖ Pre-anesthetic medications:

1. Sedatives and hypnotics:

- Example: Diazepam, lorazepam and midazolam. (Midazolam is potent and short acting)
- sedative, amnesic, anxiolytic effects and wide margin of safety
- Muscle relaxation.
- Reduce amount of anesthesia. .
- Do not cause postoperative nausea and vomiting.
- They are useful for procedures e.g. endoscopies, & Cardiac catheterization

2. **Narcotic analgesics**: such as morphine, pethidine or fentanyl

- Produce analgesia and sedation.
- Reduce amount of anesthesia.
- **Disadvantage** : depression effect respiratory, cause postoperative nausea and vomiting.

3. **Anticholinergics:** Atropine, hyoscine and glycopyrrolate.

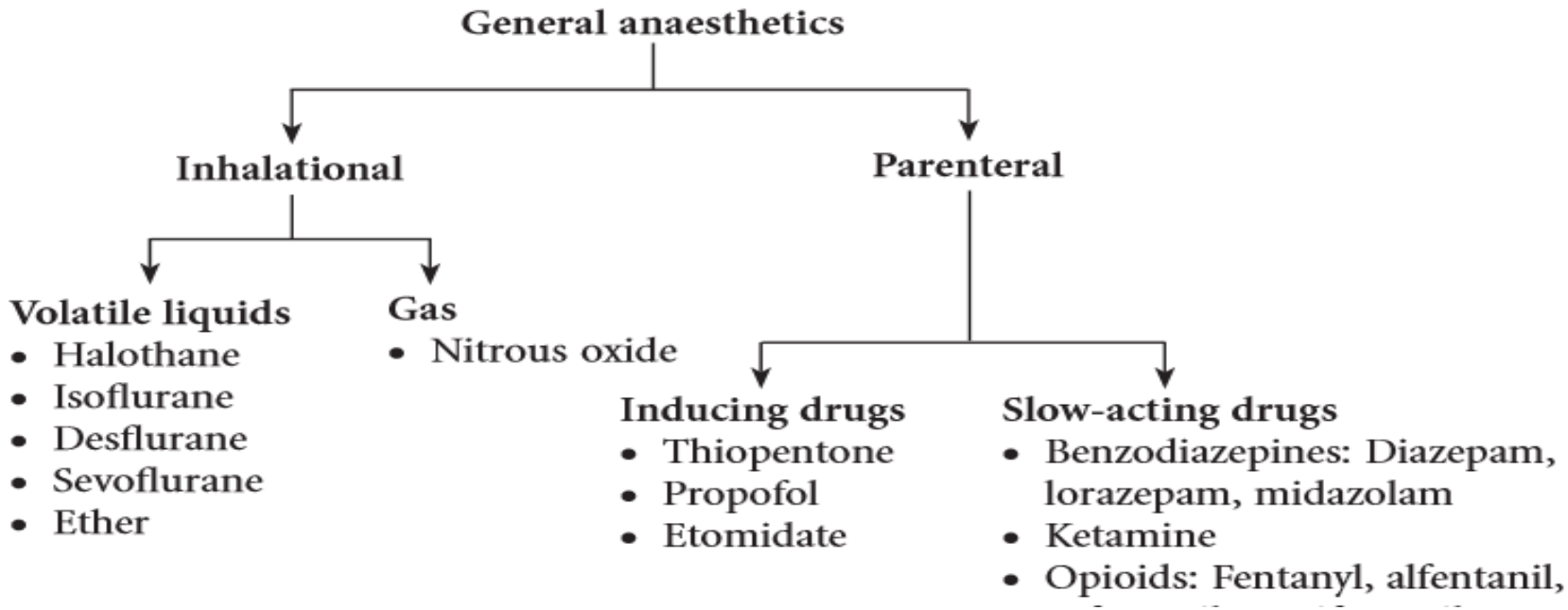
- Reduce salivary and bronchial secretions.
- Counteract bradycardia and respiratory depression.

4. **Antiemetics:** As metoclopramide, domperidone or ondansetron.

5. **Skeletal muscle relaxants**: (Neuromuscular blockers): As succinylcholine, atracurium
   - facilitate tracheal intubation & surgery.
   - It is blockade of nicotinic acetylcholine receptors in the neuromuscular junction

6. **To prevent acid secretion and stress ulcer**:
   - H2-Blocker such as ranitidine or proton-pump inhibitor like omeprazole
   - reduce gastric acid secretion especially before prolonged surgery

General anesthesia



❖ Mechanism of action of general anaesthetics

- ❑ Depress reticular formation by enhancing the activity of inhibitory transmitters (GABA) and blocking the activity of excitatory transmitters (glutamate).

- ➢ **Halogenated inhaled anesthetics, barbiturates, benzodiazepines, etomidate, and propofol** → stimulate GABA A receptors
- ➢ **Ketamine and nitrous oxide** → inhibition of NMDA glutamate receptors. and Stimulates sigma opiate receptors
- ➢ **Opioids (fentanyl)** → Stimulates mu opiate receptors

1. Intravenous anesthesia:

- Given by slow intravenous injection for rapid induction of anaesthesia → then replaced by inhalational anaesthetics for longer-term maintenance of anaesthesia
- Easy & simple administration (they do not need special device or medical skills)
- Rapid induction and recovery & short duration, without post-anesthetic vomiting.
- No irritation of respiratory tract as inhalation anesthesia.
- **Disadvantages** is that once administrated cannot be withdrawn and they are not suitable for long operations because of relative short duration of action.

❖ Preparation:

1- **Ultrashort acting Barbiturates**: as Thiopentone

- High lipid solubility → rapid onset (rapid crossing of BBB) and short duration (redistribution from the brain to other highly perfused tissues) → rapid recovery
- **Used** as i.v. anaesthetic for induction anesthesia in short operations
- **Disadvantages/adverse effects of thiopentone** (narrow safety margin):
  - Cardiovascular and respiratory depression,
  - Poor analgesic, Poor muscle relaxant, Causes laryngospasm, Bronchospasm and apnea
  -Thiopental (Highly Alkaline) is NOT mixed with Succinylcholine (Acidic).

General anesthesia

Propofol

- Acts as thiopental. ↑ GABA-A transmission.
- Rapid onset (30 - 40 seconds) and Rapid recovery.
- Widely used IV anesthetic for induction, also can be used for maintenance by IV infusion
- It is widely used and has replaced thiopental as the first choice for induction of general anesthesia and sedation.
- **Advantage**: antiemetic (↓ risk of post operative vomiting)
- **Disadvantages**

  - Respiratory center depressant less than thiopental.
  - Markedly decreases the blood pressure with weak analgesia.

Etomidate:

- It is a hypnotic agent used to induce anesthesia, with weak analgesia activity
- Acts as thiopental with shorter duration of action.
- Minimal Respiratory & CVS effects.
- Suitable for patients with cardiovascular or respiratory dysfunction.
- **Side effects**: Nausea, vomiting and pain at site of injection.

Ketamine (Dissociative Anesthesia)

- Acts as antagonist of NMDA receptors and stimulation of σ opiate receptors
- a short-acting iv anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake), sedation, amnesia, marked analgesia.

- Induces profound analgesia → used for dressings of bums & minor procedures in children (also be given IM).
- The only intravenous anesthetic → produces cardiovascular stimulation through central sympathetic stimulation (↑ Bl.P. H.R and C.O.) → beneficial in cases of shock.
- No respiratory depression and has a potent bronchodilator effects. → beneficial in asthmatics

- **Side effects**:
  - ↑ HR, BP and Intracranial pressure, cardiac output and skeletal muscle tone,
  - Hallucinations during recovery.

- **Contraindicated** in cases of hypertension.

❑ **Opioid Analgesics**

- They include fentanyl, and pethidine
- They are potent analgesics and can be used along with anaesthetics → to decrease the requirement of anaesthetic

Intravenous anesthetics

	Barbiturates	Benzodiazpines	Etomidate	Opoids Fentanyl	Ketamine	Propofol
Induction	rapid	slow	rapid	Slow	Moderate	**rapid**
Recovery	Moderate+ vomiting	slow	Moderate + vomiting	Slow	Moderate	**Very rapid**
Vomiting	Frequent	Antiemetic	Frequent	Frequent	Frequent	**Anti-emetic**
Pain sensation	Anti-analgesic	-----	----------	analgesic	Analagesic	---
Amnesia	----	++		+ partial	++ Dream like state&dissociative anesthesia	
Heart	Depression				Stimulation, Tachycardia	**Bradycardia**
Blood vessels	Dilatation				Constriction	**Dilatation**
Blood pressure	Decrease				Increase	**Decrease**
Respiratory center	Depression especially in fetus if taken during pregnancy	Slight depression		Depression + respiratory muscle rigidity		**depression**
Bronchi		-----	----	**Spasm**	**Dilatation**	

Dr. Mohammed Al-khawlani

	Barbiturates	Benzodiazpines	Etomidate	Opoids Fentanyl	Ketamine	Propofol
Other organs	Antiepileptic	Antiepileptic				
Local reaction	Pain & thrombosis		Pain		Psychosis & nightmares	
Clinical uses	**Induction of general anesthesia and eye operations because it reduce intraocular pressure**	**Treatment of Status epilepticus**	**Deep sedation in critically ill patients& Anesthesia in cardiac patients**	**Minor cardiac surgery**	**Pediatric surgery Contra-indicated in old age& psychiatric patients& not used in induction due to less rapid onset**	**Short operations due to rapid recovery Without vomiting**

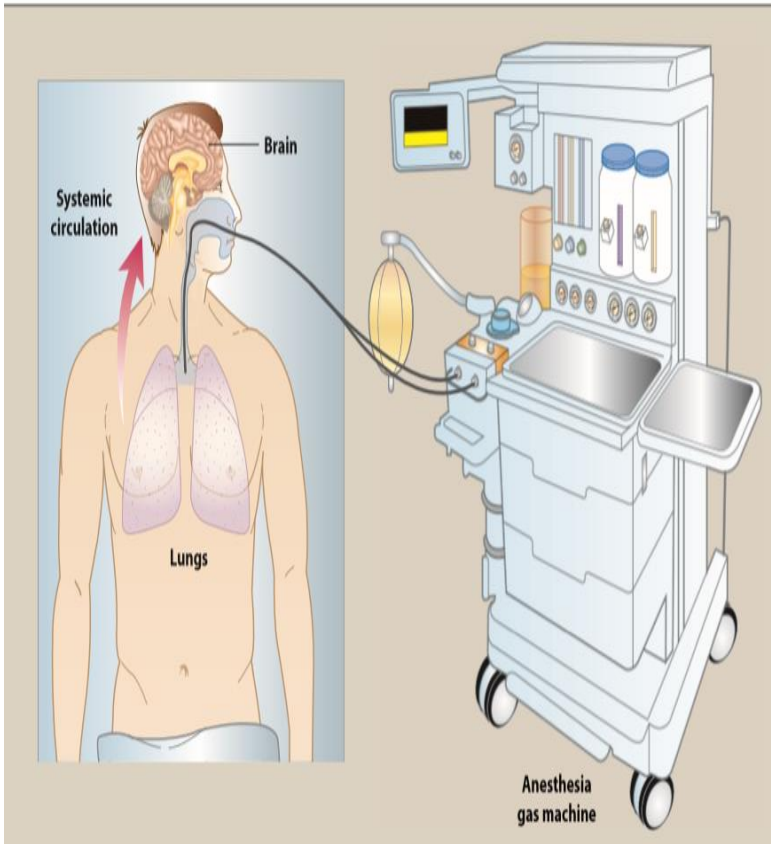
❖ Inhalational Anesthetics

- They are: - volatile liquid (e.g. halothane, isoflurane, desflurane, sevoflurane)
  - gases (e.g. Nitrous oxide)

- Acting by increasing the effect of GABA and also by blocking of NMDA receptors and nicotinic receptors in brain.

▪ Properties of an ideal inhalational anaesthetic

- Nonflammable and nonexplosive
- Minimal interactions with other drugs.
- Less side effects on respiratory, cardiovascular and Hepatic.
- High lipid solubility.
- Low blood solubility → rapid induction &recovery
- Nontoxic, nonirritant to the airways, and no unpleasant odour.
- Has Analgesic activity.
- Inexpensive



- **Anaesthetic potency** of the inhaled anaesthetics is measured as the minimum alveolar concentration (MAC) → Anesthesia in 50% of patients, It indicates the potency of inhalational general anaesthetics.

  - The lower MAC = The more potent anesthetic. (As Halothane)
  - Higher MAC → low potency. (As nitrous oxide)

- Factors that can decrease MAC (make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis.

❖ Pharmacokinetics

- Alveolar air → Absorbed → Pulmonary veins → Heart → Arteries → Tissues specially brain → Veins → Heart → Pulmonary artery → Alveolar air → Excretion.
- Redistribution from brain to fatty tissue leading to termination of action
- Speed of induction (Rate of onset) and recovery depends on the solubility of the anaesthetic agent in blood
  - Anesthetics highly soluble in blood e.g. Halothane → Slow rates of induction & recovery.
  -Anesthetics with low solubility in blood e.g. Nitrous oxide →Rapid rates of induction & recovery.
- Slow removal from the body by renal excretion

➢ **Nitrous oxide:** gases

- Non-irritant , Non-inflammable, Non-Explosive
- Rapid onset of action and recovery.
- Low potent as anesthetic. (MAC ≥ 100%)
- Good analgesia used 30 - 50% in combination with oxygen for analgesia, in dentistry & in obstetric analgesia.
- Safest inhalation agent: less cardiac or respiratory depression- less uterine relaxation-no hepatitis- no malignant hyperthermia.

- **Disadvantages:**

  - Weak anesthetic action & skeletal muscle relaxation , Should be used in combination with other anesthetics. (as halothane)
  - Diffusion hypoxia. During recovery → Rapid diffusion from Blood to alveolar air → Prevent the access of oxygen (need sufficient oxygen during recovery)

➢ **Halothane:** volatile liquid

- Non-irritant to respiratory tract. Non-Inflammable, Non-Explosive
- High potent as anesthetic. (MAC= 0.75%)
- It is a potent bronchodilator and is preferred in asthmatics
- It is potent uterine relaxants, used for treatment oxytocic effect of oxytocin

- Halothane is not hepatotoxic in children (unlike its potential effect on adults), it is suitable in pediatrics for inhalation induction (sevoflurane is now the agent of choice)
- Uses induction and maintenance of general anesthesia.
- No postoperative nausea and vomiting

❖ **Disadvantages:**

- Weak analgesia & muscle relaxation → Coad ministered with nitrous oxide, opioids
- Hypotension: (Direct VD)
- Respiratory depression.
- Delayed hepatic toxicity
- Idiosyncrasy: Malignant Hyperthermia. (Treat by IV Dantrolene)
- Cardiotoxic: bradycardia, arrhythmia (↑ sensitization of the heart to catecholamines) .

➢ **Isoflurane:** volatile liquids.

- Induction and recovery are rapid than halothane,
- Better muscle relaxation.
- Less respiratory, cardiac or hepatic toxicity than halothane.& Uterine relaxant
- Uses for maintenance of general anesthesia.
- **Disadvantages:** It has a pungent odor and stimulates respiratory reflexes (for example, breath holding, salivation, coughing, laryngospasm) and is therefore not used for inhalation induction, it produce hypotension, irritant on bronchi → bronchospasm

➢ **Desflurane:** volatile liquids

- very rapid onset and recovery due to low blood solubility.
- Less respiratory, cardiac or hepatic toxicity than halothane.
- Like isoflurane, It has a pungent odor and stimulates respiratory reflexes and is therefore not used for inhalation induction.
- It is relatively expensive and used for maintenance of general anesthetics
- Desflurane is irritant to bronchi → bronchospasm

➢ **Sevoflurane:** volatile liquids

- It is bronchodilator, not irritant and has a rapid onset and recovery
- suitable for induction & maintenance of general anesthetics in children & adults
- Less irritant to bronchi than Desflurane.
- sevoflurane produce renal impairment on repeated administration due to release of fluorine ion

	Halothane	Isoflurane	Desflurane	Sevoflurane	Nitrous oxide
Cost	Cheep	Moderate	Moderate	Moderate	**Cheep**
Physical properties **-Inflammability** **-explosive**	No No	No No	No No	No No	**No** **No**
Anesthetic action	Potent	Potent	Potent	Potent	**poor**
Induction and recovery	Slow	rapid	rapid	rapid	**rapid**
Analgesic effect	Inadequate	Inadequate	Inadequate	Inadequate	**adequate**
Skeletal muscles relaxation	Inadequate	adequate	adequate	adequate	**No relaxant**
C.V.S	arrhythmias, bradycardia, hypotension	less than halothane hypotension	---------- hypotension	---------- hypotension	---------- ----------
Hepatic function	**Autoimmune hepatitis**	--	--	--	--

	Halothane	Isoflurane	Desflurane	Sevoflurane	Nitrous oxide
Respiratory system	Non-irritant, bronchodilatation and is preferred in asthmatics	bronchospasm; irritâtes air passages	bronchospasm; irritates air passages	Non-irritant, bronchodilatation	----------
Uterus	Relaxation	Relaxation	Relaxation	Relaxation	--
Uses	**Not pungent, well tolerated— preferred for induction and maintenance in children**	**Commonly used for maintenance anaesthesia • not cause seizures • No renal toxicity**	▪ **used for maintenance anaesthesia** ▪ **not cause seizures** ▪ **No renal toxicity •**	▪ **Suitable for induction and maintenance of anaesthesia in children** ▪ **Suitable for cardiac and respiratory patients**	**Used in maintenance of anesthesia - in obstetric analgesia**

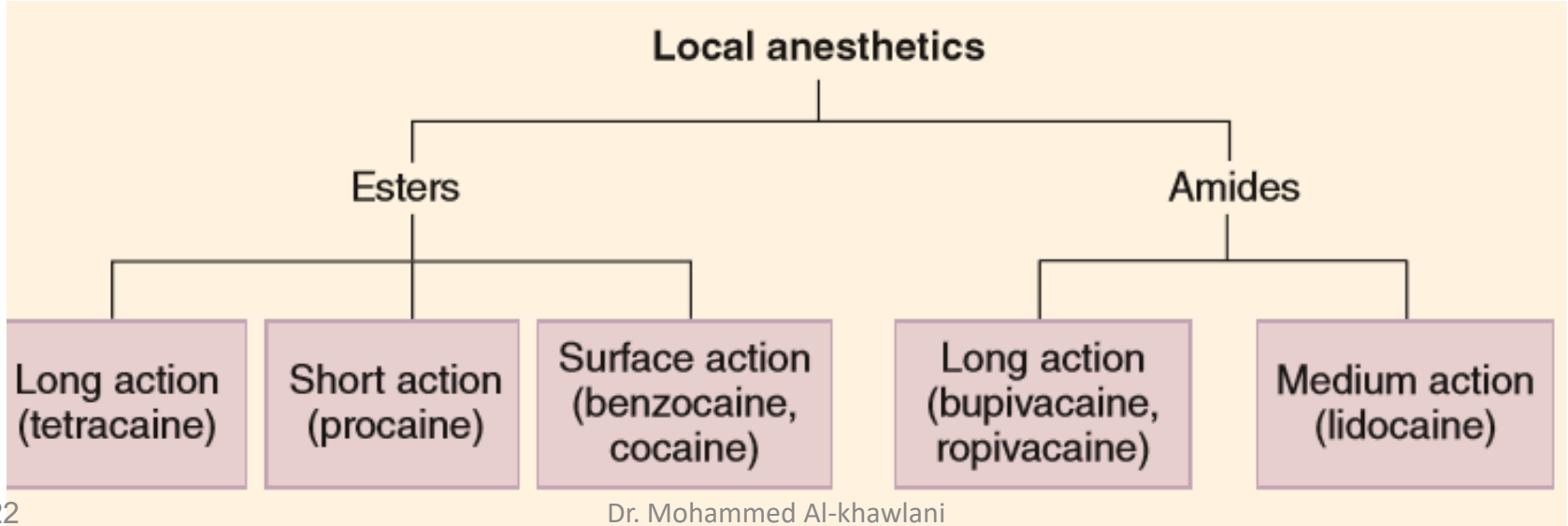
	Halothane	Isoflurane	Desflurane	Sevoflurane	Nitrous oxide
Disadvantages	Hypotension, Respiratory depression. Both Hepatotoxicity and malignant Hyperthermia , arrhythmias	Pungent odour—hence not commonly used for induction	Pungent odour—hence not commonly used for induction	renal toxicity	Second gas effect and diffusion hypoxia occur with N2O only

Local anesthetics

Local anaesthetics

- Local anaesthetics (LA) are drugs that induces a reversible loss of pain sensation in a specific area of the body without loss of consciousness.
- Drug that blocks nerve conduction at all types of nerves (sensory > autonomic > motor) nerves

- There are two classes of local anesthetics: amides and esters
- The primary differences between the two classes are in their relative metabolism and their potential for allergic reactions (esters more than amides).



Classification of local anesthetics:

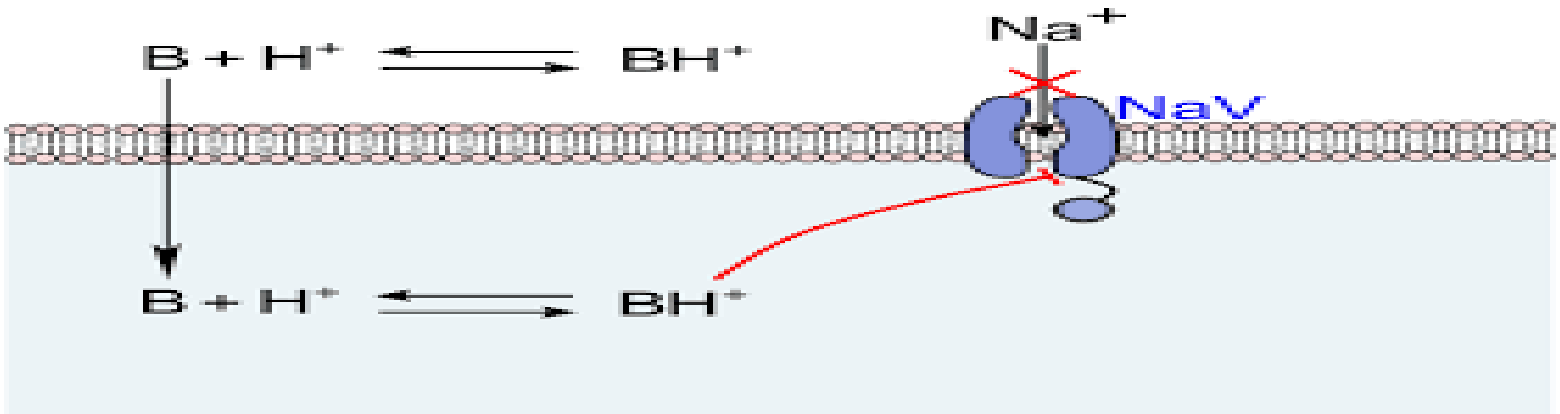
	Ester	Amides
Chemistry	Weak base consists of aromatic group and basic amine group linked by either Ester COO^- linkage	amide NHCO linkage
Metabolism	By plasma pseudocholinesterase	By hepatic amidase
Action	Short duration	Long duration
Allergic reaction	Frequent due to formation of para-amino benzoic acid (PABA) metabolites	Less frequent (More liable to induce systemic toxicity)
	Used parenterally and topically except - - procaine (Slow tissue penetration not used for surface anesthesia). - Benzocaine: Low solubility (can not be prepared in injection form→ used as a surface anesthetic only) - Cocaine: Used only in surface anesthesia (limited use due to abuse potential).	Used parenterally and topically - - Lidocaine: Intermediate acting (2h)., Rapid penetration: 1st choice for surface anesthesia. can be used IV in cardiac arrhythmia - bupivacaine: Long duration (3h); due to high binding to plasma protein. Moderate tissue penetration. - Ropivacaine: Long duration. More selective on sensory than on motor nerves.
Preparations	cocaine, procaine, tetracaine and benzocaine	lidocaine, bupivacaine, mepivacaine and ropivacaine

According to clinical use

a. **Surface anaesthetics:** Cocaine, Lidocaine:, tetracaine, benzocaine.
b. **Injectable anaesthetics:**
i. Short acting with low potency: Procaine.
ii. Intermediate acting with intermediate potency: Lidocaine, mepivacaine, prilocaine.
iii. Long acting with high potency: Tetracaine, bupivacaine, ropivacaine.

❖ Mechanism of action:

- After application of local anesthetics → hydrolyzed to non-ionized and ionized base. →Non ionized base penetrates cell → Inside the cell membrane, change to ionized form →block Na+-channel by binding to inner (inactivating) gate of sodium channels → ↓ Impulse generation & Propagation



❖ Pharmacological actions

- **C.N.S.** → Stimulation (Especially Cocaine) and then depression in higher doses. They cause excitement, tremor, twitching, restlessness and convulsions. Large doses can cause respiratory depression, coma and death.

- **C.V.S:**

a. **Heart**: LAs, → Blockade of cardiac sodium channels →↓ abnormal pacemaker activity, contractility, conductivity, excitability, heart rate

- At higher concentrations, the intravenous administration of LAs may precipitate cardiac arrhythmias.
- Bupivacaine is more cardiotoxic than other LAs→ may cause cardiovascular collapse and death.
- Lidocaine →↓ automaticity and is useful in ventricular arrhythmias.

b. **Blood vessels**: All local anesthetics cause hypotension except cocaine which causes hypertension due to inhibition of norepinephrine uptake from sympathetic neurons.

❖ Factors affecting local anesthetic action

- pH dependent and the penetrability of LA is increased at alkaline pH (i.e. when the unionized form is more).
  - At acidic pH (in infection, pus, inflamed areas) → ↓ penetration of local anesthetics to site of action → less effective

- **Type of nerve** :- Myelinated nerves are more readily blocked by local anesthetics than non mylinated ones .
  -LA are more active against stimulated nerves (during painful condition) than resting nerve (non painful conditions).

- **Lipid solubility:** Higher the lipid solubility more is the potency of the drug, Bupivacaine is 7 times more lipid soluble than lidocaine therefore more potent.

- **Addition of Adrenaline** → V.C.→↓ Absorption of L.A. (except cocaine) → ↑ Duration, ↓ Toxicity & ↓Bleeding.

NB: Vasoconstrictors are **CI** in anesthesia of fingers, toes & nose → gangrene.
Felypressin (V1 vassopressin receptor agonist) is preferred in cardiac patients (no effect on HR& BP).

Local anesthesia

❖ Method of application and therapeutic uses of local anesthetics

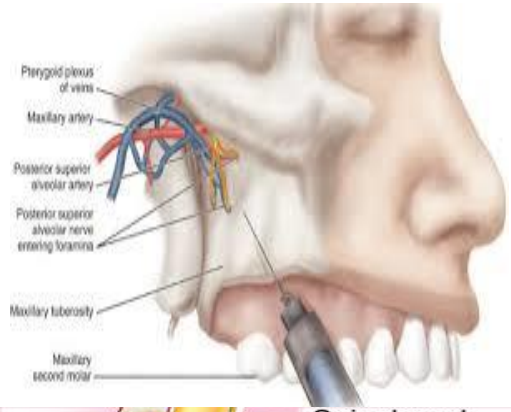
	Therapeutic uses	Preparation
Surface anesthesia	-Applied on the surface of skin or mucous membrane in -Minor eye operations -Ulcers in skin & mucous membrane	-Lidocaine , tetracaine for mucous membrane -Benzocaine spray for skin ulcers& throat lozenges.
Infiltration anesthesia	-Field block : injection SC around the area to be anesthetized (field of operations) e.g. dental procedures -Nerve block : injected SC around nerve trunk supplying the area to be anesthetized Used in dental , cutaneous, eye operations	Most of local anesthetics Articaine , lidocaine , ropivacaine
Central nerve block	-Epidural : Injection in epidural space. It is used for obstetric analgesia , lower abdominal surgery -Spinal cord : Injection in subdural space .It is used for lower abdominal surgery	Epidural: lidocaine, bupivacaine, ropivacaine + opioids Spinal: most of local anesthetics





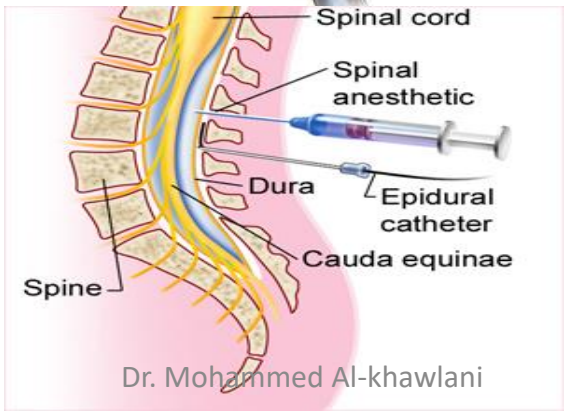
Field block anesthesia





Nerve block nesthesia





Spinal & epidural anesthesia

Local anesthesia

❖ Side effects of local anesthetics

- **CVS**: Bradycardia, hypotension, cardiac arrhythmias, rarely cardiovascular collapse and death. Bupivacaine is highly cardiotoxic. Ropivacaine is the least one.

- **CNS:** LAs initially cause CNS stimulation followed by depression. They are restlessness, tremor, headache, drowsiness, confusion and convulsions followed by respiratory depression, coma and death.

- **Allergic reaction :**
  - skin rashes, itching, erythema, urticaria, wheezing, bronchospasm and rarely anaphylactic reaction, More with ester than amide local anesthetics .It is related to para-aminobenzoic acid metabolites

- **Blood :**
  - Prilocaine produce cyanosis because it combines with hemoglobin forming non-functioning methhemoglobin.

- **Spinal anesthesia**: can lead to hypotension, headache, respiratory depression and meningitis.

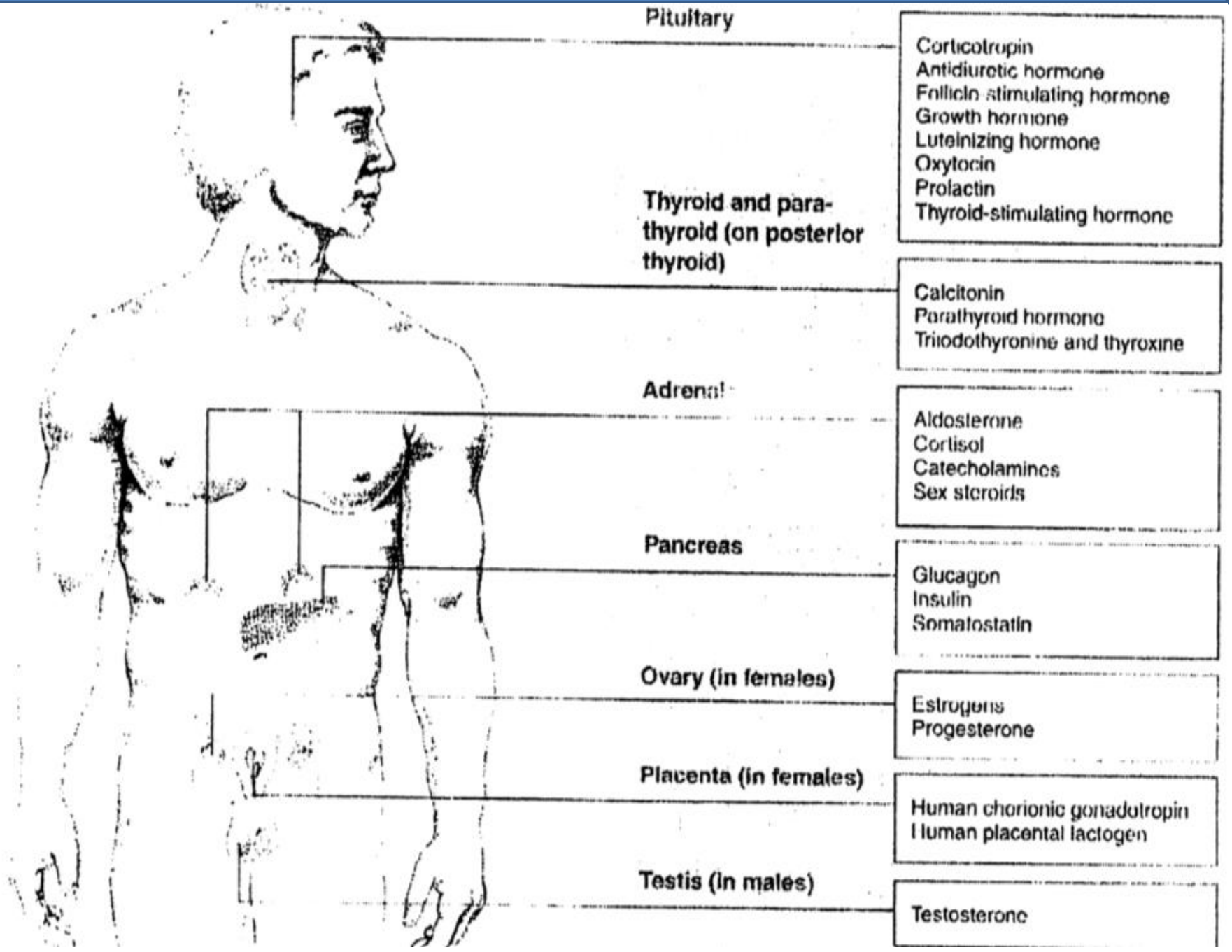
- **Epidural anesthesia**: have fewer side effects.

Drugs affecting the endocrine system (Hormones)

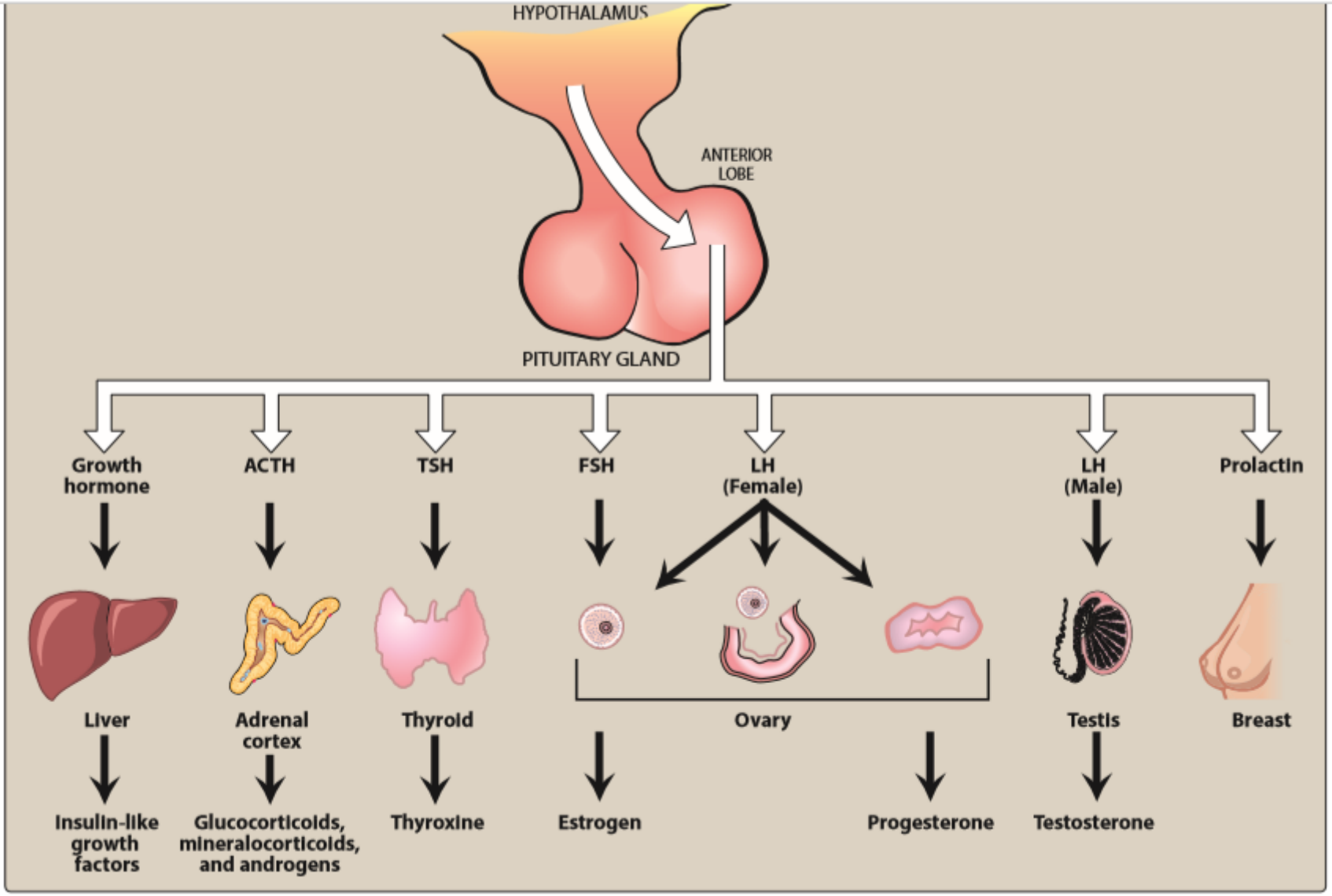
Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Endocrine glands and Hormones



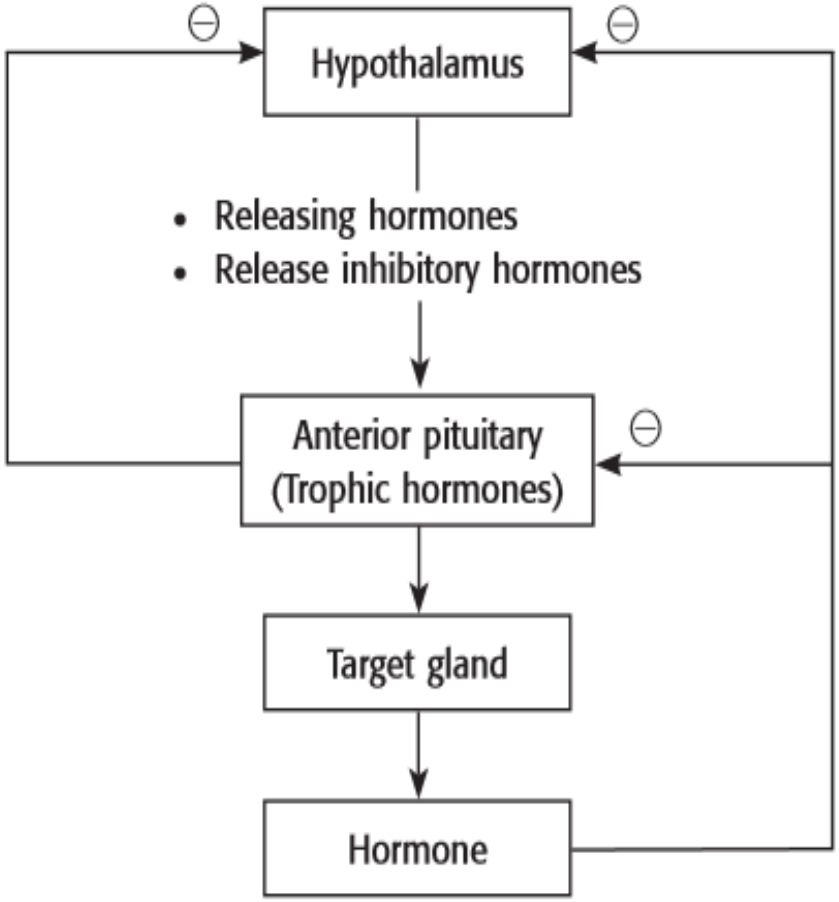
Hypothalamic & Pituitary Hormones



Anterior pituitary hormones. ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; FSH = follicle stimulating hormone; LH = luteinizing hormone.

Hypothalamic & Pituitary Hormones

- Hypothalamus produces releasing and inhibitory hormones → control pituitary secretion → carries the releasing and inhibitory hormones.



Thyroid Hormones and Antithyroid Drugs

Thyroid gland

- It is a large endocrine gland situated in the base of the neck
- Have 2 types of hormones:
  - **Triiodothyronine** (T3) and **thyroxine** (T4) → for regulation of energy level, metabolism and mental, physical development (growth).
  - **Calcitonin** → regulating calcium metabolism.

❖ Steps of synthesis and regulation of thyroid hormones:

1. TRH from the hypothalamus stimulates the anterior pituitary to synthesize TSH (stimulation of iodide trapping and synthesis of thyroid hormones, and increases the size and vascularity of the gland).

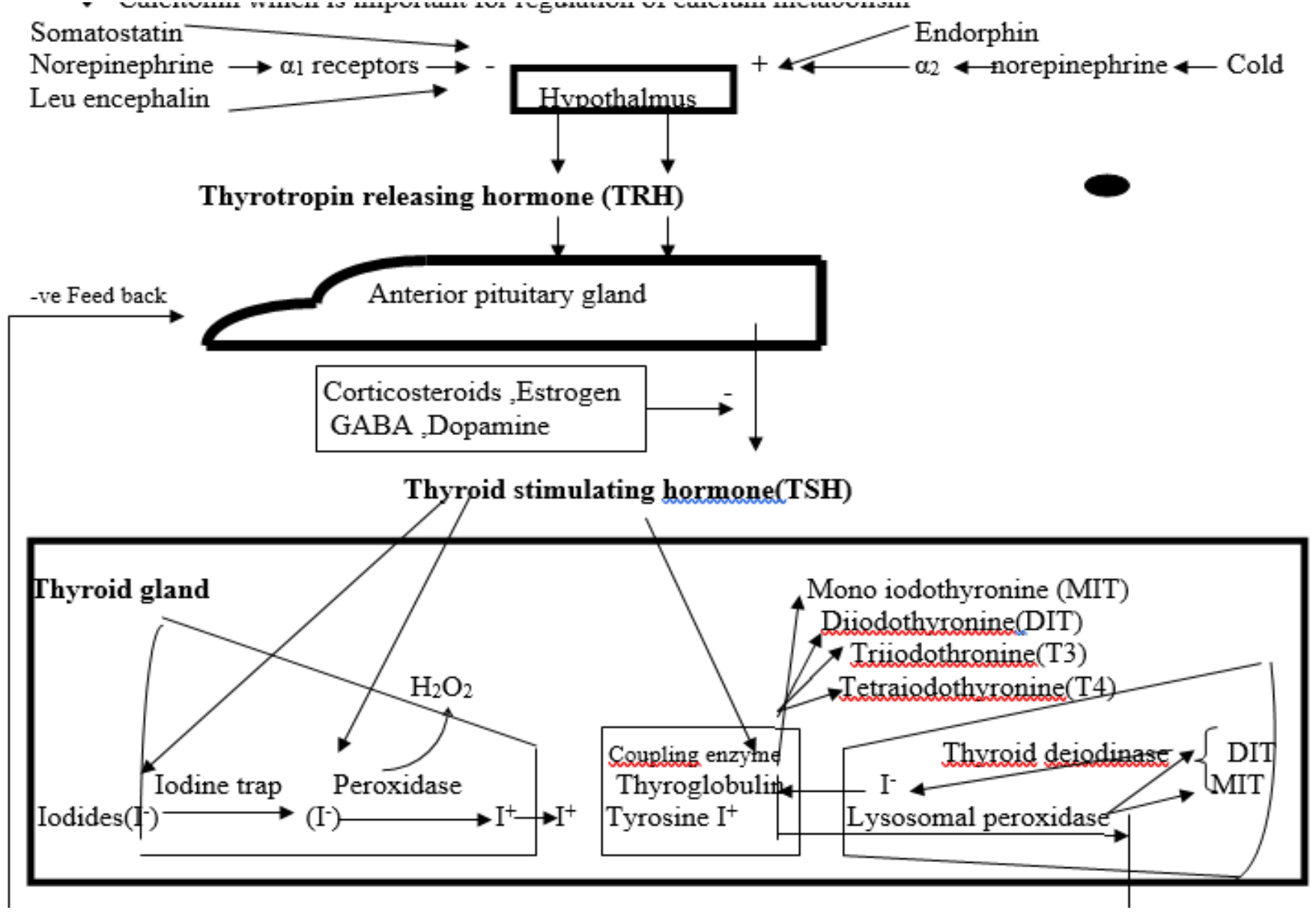
2. **Iodide trapping:** active uptake of iodide into follicular cells, stimulated by TSH. and inhibited by thiocyanates and perchlorates, which compete with iodide

3. **Oxidation:** Iodide is oxidized into iodine by peroxidase enzyme, inhibited by thiourea group of antithyroid drugs.

4. **Organification and Coupling of iodine:** iodine binds to tyrosine to form MIT and DIT: Two molecules of DIT couple to form **thyroxine** (T4), and one molecule of MIT with one molecule of DIT forms **triiodothyronine** (T3).

Thyroid Hormones and Antithyroid Drugs

❖ Steps of synthesis and regulation of thyroid hormones:



Thyroid Hormones and Antithyroid Drugs

5. Hormone release: proteolysis of thyroglobulin by protease enzyme → release of T4, T3. These process is inhibited by high levels of intrafollicular iodide.

6. Peripheral conversion of T4 to T3: Most of the hormone released from thyroid is T4, which is much less potent in comparison to T3. Conversion of T4 to T3 in periphery is inhibited by propylthiouracil, propranolol.

❖ Mechanism of action of thyroid hormones:

1) T3 enter the nucleus and bind to specific receptors which stimulate protein synthesis and various enzymes necessary for metabolism.

❖ Pharmacological actions:

1. **Calorigenic action**: increase oxygen consumption, heat production, an sweating , increase glucose absorption, (hyperglycemia), decrease lipogenesis, and decrease cholesterol level in blood.

2. **Growth:** essential for mental, physical, and sexual development both directly and indirectly by stimulation of release and effect of growth hormone.

3. **CVS:** increase number and sensitivity of B1-receptors (supersensitivity and upregulation) → cardiac stimulation.

4. **GIT**: increase cholinergic activity of GIT → stimulation of motility and secretion.

5. **CNS stimulation**

- **Deficiency of thyroid hormones** in:
  - Children results in cretinism characterized by mental retardation and other features of hypothyroidism
  - Adults, it results in myxedema.

- **Hypersecretion** of these hormones also has effects on various organ systems resulting in 'thyrotoxicosis'.

Thyroid Hormones and Antithyroid Drugs

❑ **Hypothyroidism:** (↓ thyroid hormone secretion)

- Hypothyroidism (autoimmune destruction of the gland or by ↓ TSH secretion, also by iodine deficiency.

- **Symptoms:** Bradycardia, Goiter (Thyroid enlargement), Poor resistance to cold, ↓ Mental and physical development, Weight gain. (myxedema and myxedema coma in adults, and cretinism in children).

➢ **Treatment:** as

1. Levothyroxine (T4)
   - synthetic-T4: less potent than T3- delayed onset because of long t 1/2 (7 days).
   - It is the preparation of choice: cheap -stable -well absorbed -long acting.

2. Liothyronine (T3)

   - Synthetic T3: 4 times as potent as T4- rapid onset because of shorter t 1/2 (1.5 days), so it is used in emergencies as myxedema coma I.V.
   - High cost. (not commonly available).

Thyroid Hormones and Antithyroid Drugs

❖ **Therapeutic uses:** Replacement therapy in hypothyroid states

1. Cretinism and myxedema:
2. Myxedema coma: This is a medical emergency and usually common in untreated myxedema cases. It is treated with levothyroxine, intravenously (i.v.) .

NB: Hypothyroidism may be prevented by adding iodine to commonly used foods. (usually salt and flour), The adult need about 150-200 μg of iodine daily.

- **Side effects:**
- Tachycardia and weight loss, palpitation, arrhythmia, and anginal pains. Diarrhea, Nervousness, tremors, and insomnia.

- **Drug interactions:**
- Food, calcium preparations and aluminum-containing antacids → ↓ absorption of thyroxine.
- P450 enzymes inducers (such as phenytoin, rifampin, and phenobarbital) → ↑ metabolism of thyroxine.

Thyroid Hormones and Antithyroid Drugs

❖ Antithyroid Drugs

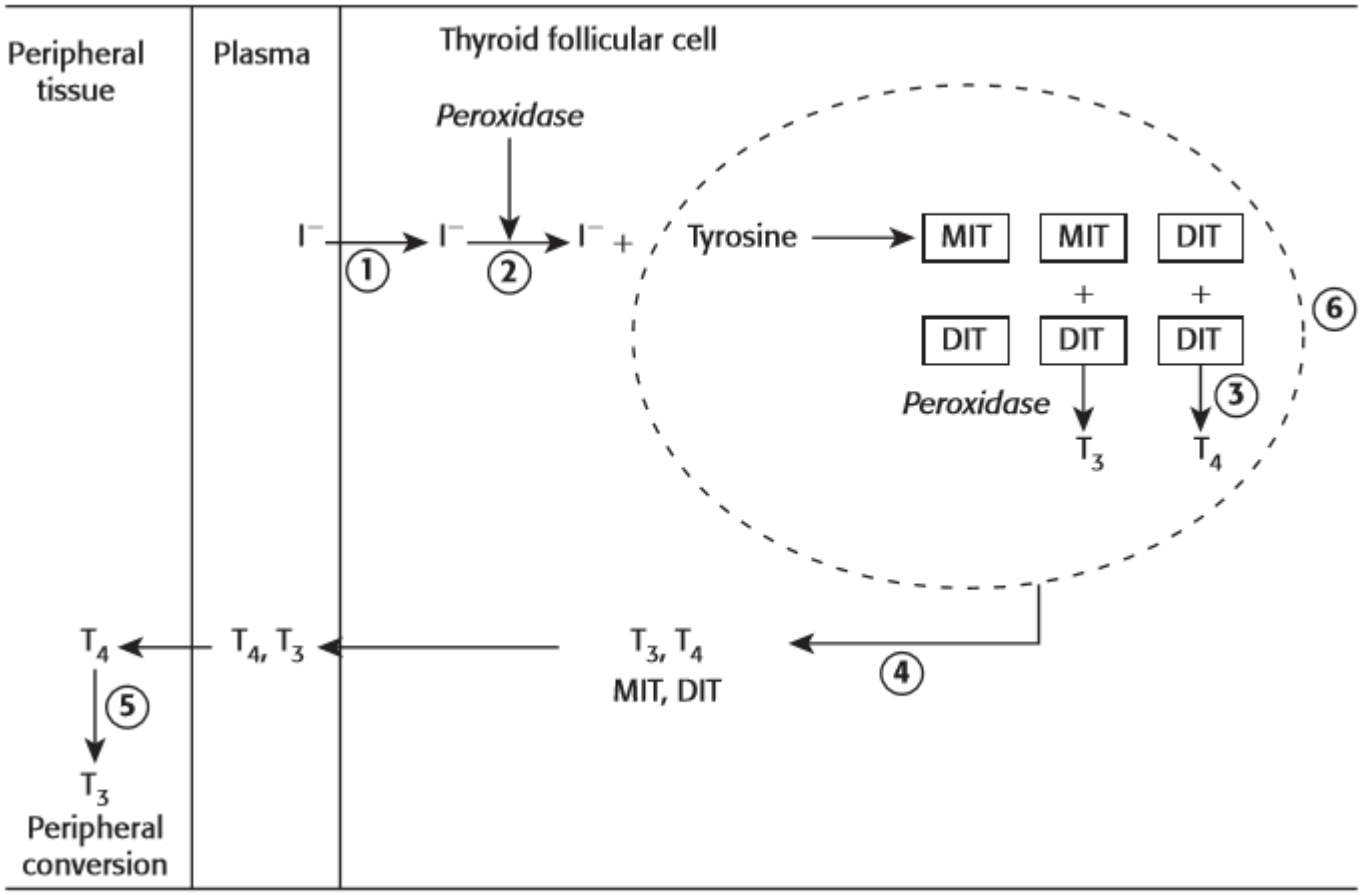
❑ **Hyperthyroidism**: Thyrotoxicosis (↑Thyroid hormone secretion)

- Hyperthyroidism: autoimmune disease (**Graves disease**) which antibodies activate TSH receptors → ↑ TSH secretion.

- **Symptoms**: Tachycardia and cardiac arrhythmias. ↑ Oxygen consumption and heat production. Nervousness and tremors. Goiter. ↑ appetite. Exophthalmos.

- **Treatment:**
  - Thyroid hormone synthesis inhibitors (thioamides or thiourea derivatives): as Propylthiouracil, methimazole, carbimazole.
  - Hormone-release inhibitors: Iodine, iodides of Na+ and K+
  - Thyroid tissue-destroying agent: Radioactive iodine (131I).
  - Others: Propranolol,.

Thyroid Hormones and Antithyroid Drugs



Synthesis, storage and secretion of thyroid hormones and drugs affecting them.
Site 1: Thiocyanates, perchlorates, excess iodides.
Sites 2 and 3: Iodides, thioamides.
Site 4: Iodides.
Site 5: Propylthiouracil, propranolol, glucocorticoids.
Site 6: Radioactive iodine (destruction of thyroid tissue).

Thyroid Hormones and Antithyroid Drugs

1. **Thioamides a**s: Propylthiouracil (PTU). , methimazole and carbimazole.

❑ MOA:

- They inhibit thyroid peroxidase enzyme, iodination of tyrosine and coupling of MIT and DIT
- Propylthiouracil also inhibits the peripheral conversion of T4 to T3.
- Clinical response appears after 3-4 weeks till the stored hormones are depleted from the gland (but propylthiouracil has faster effect, so it is used in thyrotoxic crisis).
- Carbimazole is rapidly converted to methimazole (more active).
- Methimazole has long half-life. (24 h.)
- Methimazole is preferred over PTU because it has a longer half-life, allowing for once-daily dosing, and a lower of adverse effects.
- Propylthiouracil is preferable during pregnancy because it does not cross placental barrier (because it is strongly bound to plasma protein).

- **Clinical uses**:

- Drug of choice in mild hyperthyroidism.
- Temporary control of hyperthyroidism in patients treated by radioactive iodine which has very delayed onset of action (about 2-3 months).
- PTU is also used in thyrotoxic crisis.

- **Adverse effects** as agranulocytosis, rash and edema. Hepatotoxicity (more with propylthiouracil).

- **C.I:** During pregnancy & lactation (Cretinism)

2. **Iodide:** as Lugol's iodine (5% iodine in 10% solution of KI), Potassium Iodide

- Given orally in high doses (> 6mg /day).
- Inhibition of the action of TSH on thyroid gland →decrease vascularity and size of thyroid gland and decrease iodine trapping and thyroxine release.

- **Used in** treatment of thyrotoxic crisis (Thyroid storm) (with PTU and Propranolol) or prior to thyroidectomy.
- Iodide is not useful for long-term therapy. (tolerance occur after a few weeks)

- **Adverse effects**:
- Allergic reactions (skin rash, angioedema, and anaphylaxis type).
- Chronic overdose with iodide results in iodism (headache, sneezing and irritation of eyes with swelling of eyelids, and sometimes pulmonary oedema).

- **C.I:** in pregnancy → fetal goiter

3. Radioactive iodine: I^{131}

- Therapeutically used radioactive iodine is I^{131} . Sodium iodide containing I^{123} is used for diagnostic scan.
- Administered orally in solution (as sodium I^{131}), rapidly absorbed and incorporated into storage follicles in thyroid.
- It is acting by emission of β rays and cause destruction of the thyroid parenchyma.
- The onset of action is very delayed (1-2 months) and maximal response appears after another 2 months, and the patient is temporarily treated by thioamides and propranolol until its effect appears

- Radioactive iodine is **used in hyperthyroidism** due to:.
  - if medical treatment is failed.
  - If surgical treatment is contraindicated e.g. in old age or cardiac patients.

Advantages: include easy administration, effectiveness, low expense and absence of pain.

Adverse effects: Hypothyroidism due to excessive destruction of thyroid follicles, slow acting and causes local soreness in the neck.

Contraindicated: During pregnancy. and lactation

4. **Beta blockers:** As: propranolol

- Used in thyrotoxicosis → decrease sympathetic stimulation → improvement in symptoms of thyrotoxicosis like tachycardia, palpitation and tremors.

- Propranolol is the most widely used and in high doses can prevent conversion of T4 to T3.
- Given orally and intravenously.

❖ **Uses**

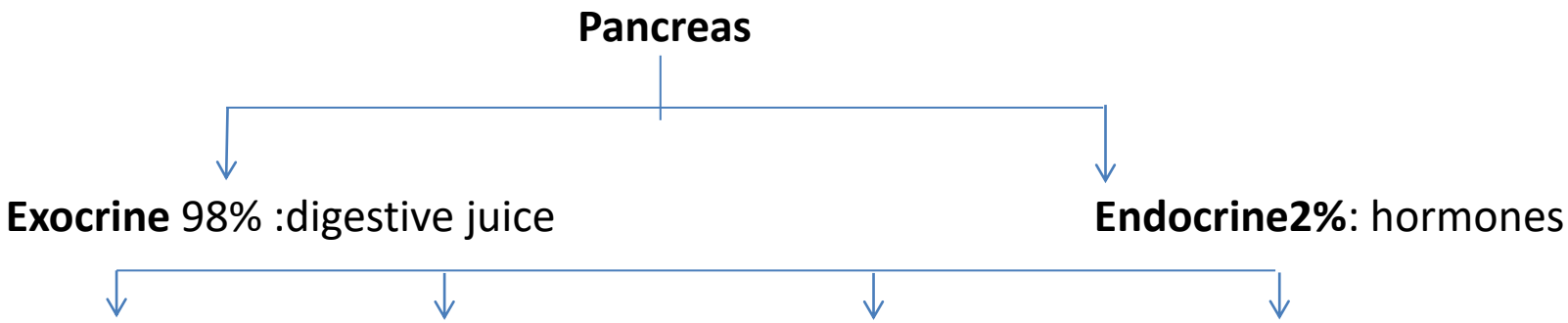
1. To control symptoms of thyrotoxicosis initially till antithyroid drugs act.
2. In thyrotoxic crisis.

❑ **Thyrotoxic Crisis (Thyroid Storm)** .

- Very high levels of circulating thyroid hormone.
- **Symptoms:** hyperthyroidism + hyperpyrexia, cardiac arrhythmias, nausea, vomiting, diarrhoea and mental confusion.
- It is usually precipitated by infection, trauma, surgery.
- Treated with propylthiouracil, iodides, propranolol and hydrocortisone

Pancreatic Hormones

Pancreatic Hormones



Delta cells 2% : **pancreatic polypeptides**	**D cells** 3%: **somatostatin**	**B cells** 75%: **- insulin -Amylin**	α cells20% **glucagon**
Increase release of digestive juice	Inhibit secretion of many hormones :insulin , glucagon , growth hormone , thyrotropin , gastrin	**Insulin**: anabolic , hypoglycemic effect **Amylin**: decrease glucose absorption from GIT -Decrease insulin secretion	Catabolic , hyperglycemic effect

Pancreatic Hormones

❑ Insulin

- Protein hormone (secret naturally from β-cells in pancreas) consists of two polypeptide chains with 51 aminoacids connected together by 2 bisulphide bridges.

❖ Regulation of insulin secretion

- **Chemical:** Glucose, amino acids and fatty acids in the blood stimulate → ↑ insulin secretion

- **Neural:**

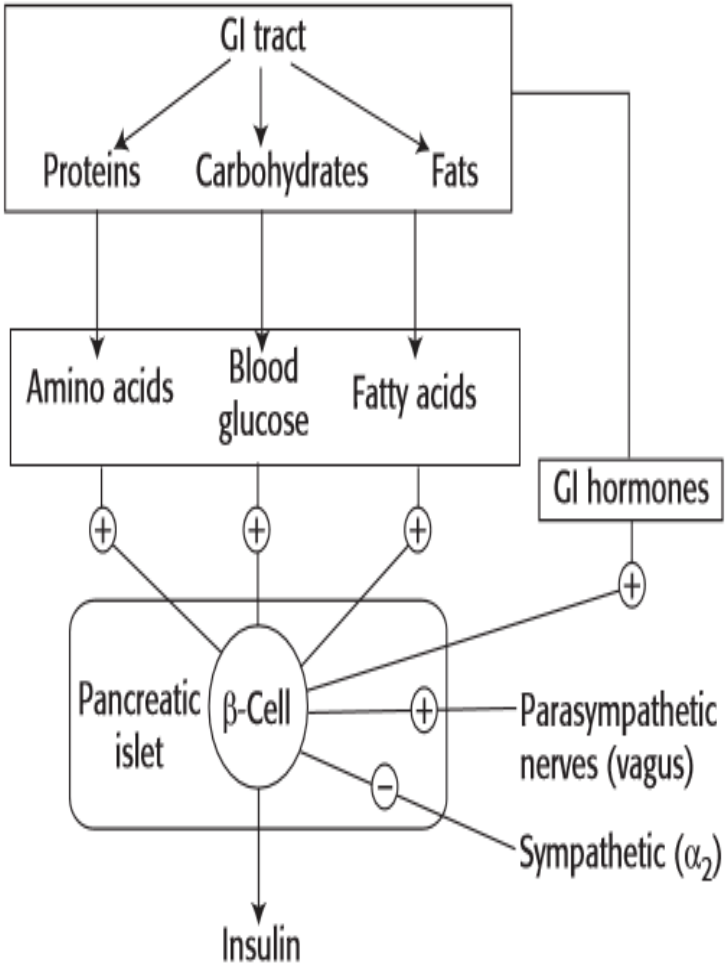
-Parasympathetic → ↑ insulin secretion and lowers raised blood sugar level.

- Adrenergic β 2 → ↑ insulin release and the blood sugar falls.

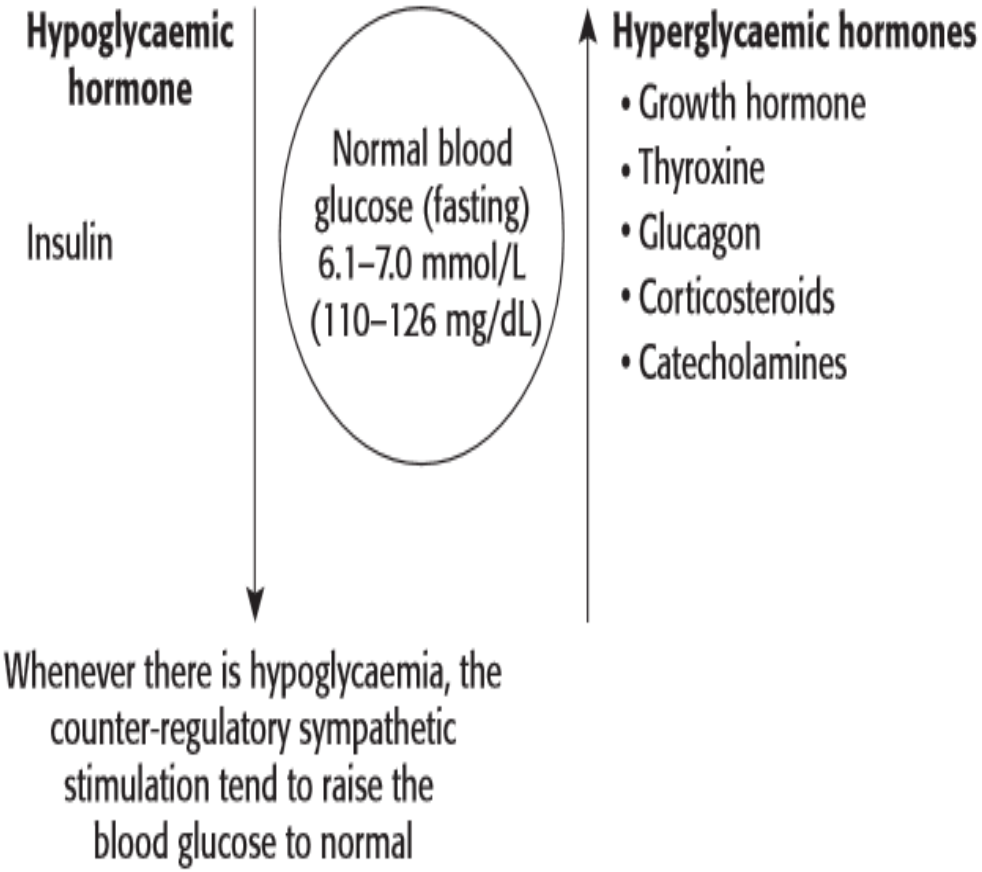
- Adrenergic α2 activation → hyperglycaemia by inhibiting the release of insulin.

- **Hormonal**: GLP-1 (glucagon-like peptide), gastrin, secretin, cholecystokinin, → ↑ insulin secretion

Pancreatic Hormones



❖ Regulation of insulin secretion


Hypoglycaemic hormone
Insulin
Normal blood glucose (fasting) 6.1–7.0 mmol/L (110–126 mg/dL)
Hyperglycaemic hormones
• Growth hormone
• Thyroxine
• Glucagon
• Corticosteroids
• Catecholamines
Whenever there is hypoglycaemia, the counter-regulatory sympathetic stimulation tend to raise the blood glucose to normal

❖ Effect of various hormones on blood glucose level.

Pancreatic Hormones

❖ Mechanism & pharmacological of action:

- Insulin binds to specific receptors (tyrosine kinase) on the cell membrane → tyrosine kinase autophosphorylation → ↑ activity of Intracellular protein kinases affecting metabolic enzymes as phosphorylase, lipase...

- **Insulin ↓ blood glucose level (Carbohydrate Metabolism) by** :
  - ↑ Utilization of glucose by peripheral tissues.
  - ↑ Synthesis and storage of glycogen in liver, skeletal muscles & adipose tissue.
  - ↓ hepatic glycogenolysis, gluconeogenesis

- Insulin deficiency in diabetes → ↑blood glucose by ↑ glucose production from liver and ↓ glucose uptake by skeletal muscle and fat cells. → glucosuria → osmotic diuresis (polyuria) → dehydration → thirst → polydipsia.

- **Insulin ↑ fat storage (Fat Metabolism) through**:
  - ↑ Plasma lipoprotein lipase → ↑ fatty acid, supply to adipose tissue. (lipogenesis).
  - ↑ Glucose uptake in fat → ↑ TGs.
  - ↓ lipolysis in adipose tissue → ↓ Free fatty acid, supply to blood.
  - ↓ Fatty acid oxidation and inhibits ketone bodies synthesis (inhibits ketogenesis).

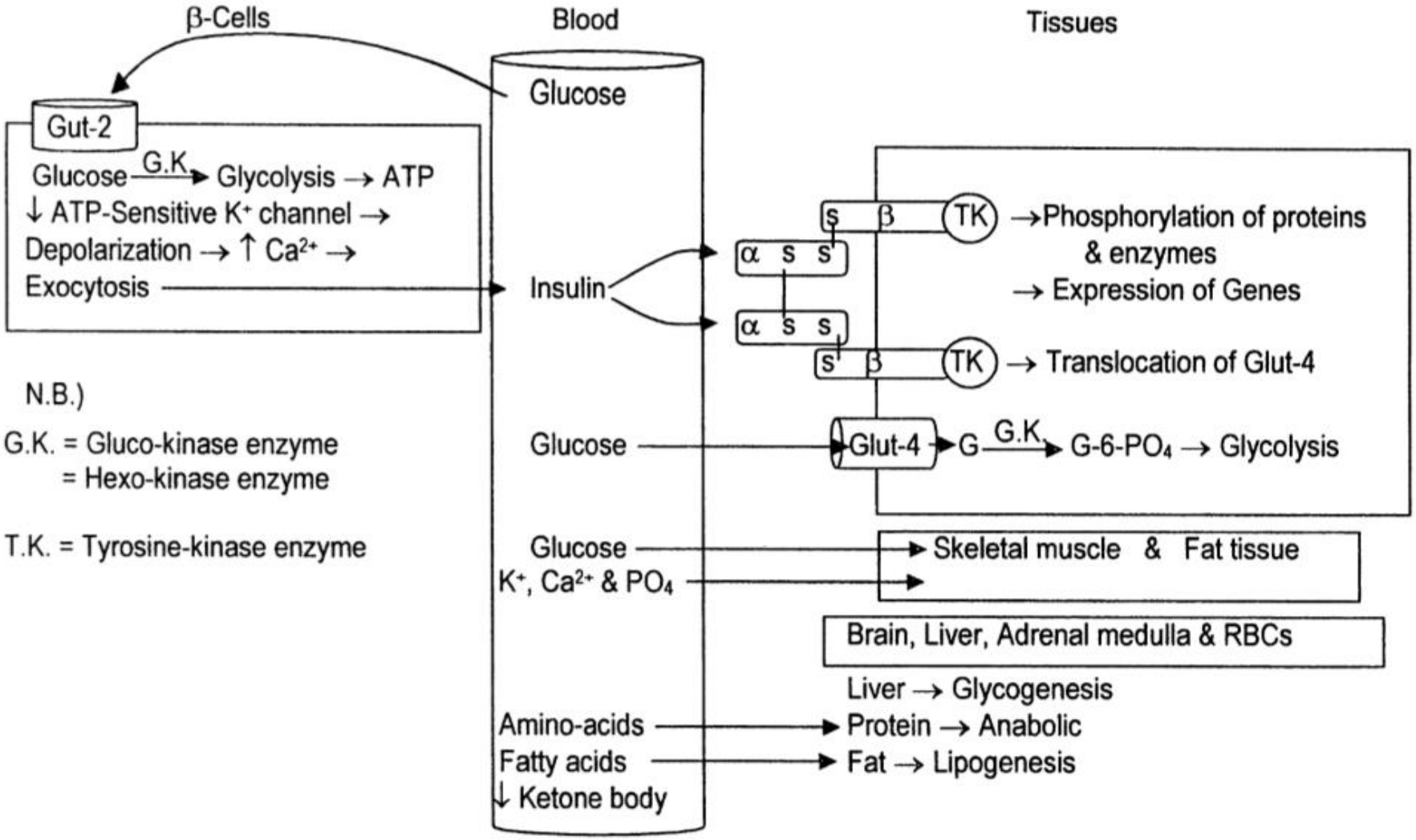
- Insulin deficiency in diabetes → ↑Lipolysis → ↑ free fatty acids in blood.
  - ↑ Oxidation of free fatty acids and formation of ketone bodies (ketogenesis).

Pancreatic Hormones

- **Insulin ↑ protein storage through**:
  - ↓ Protein break down in liver → ↑ Protein synthesis in skeletal muscle.
- Insulin deficiency → ↑ protein breakdown &↓ synthesis → muscle wasting.

- **Other actions of insulin**
  - **Stimulates transport of K+, Mg2+, and phosphate and decreases their plasma level.**
  - **Inhibition of renal sodium excretion**
  - **Promotion of learning and memory:** Insulin resistance is a risk factor for Alzheimer disease

Pancreatic Hormones



- Muscular exercise also facilitates entry of glucose into muscle cells without the need for insulin

Diabetes mellitus

- Diabetes mellitus (DM) is clinical syndrome characterized by disorder in carbohydrate, fat, and protein metabolism and hyperglycemia, due to absolute or relative insulin deficiency, or decreased sensitivity of insulin receptors.

	Normal	Impaired glucose tolerance	Diabetes mellitus
Fasting	Below 115mg /dl	116-139 mg/dl	More than 140 mg/dl
Post prandial (2 h after oral 75g glucose)	140 mg /dl	141-199mg/dl	More than 200mg/dl
HbA1C	< 6%	6 - 7%	> 7%

- **Glycated HB1c**:normal below 6 %.It gives an idea about glycemic control in the last 3 months

Diabetes mellitus

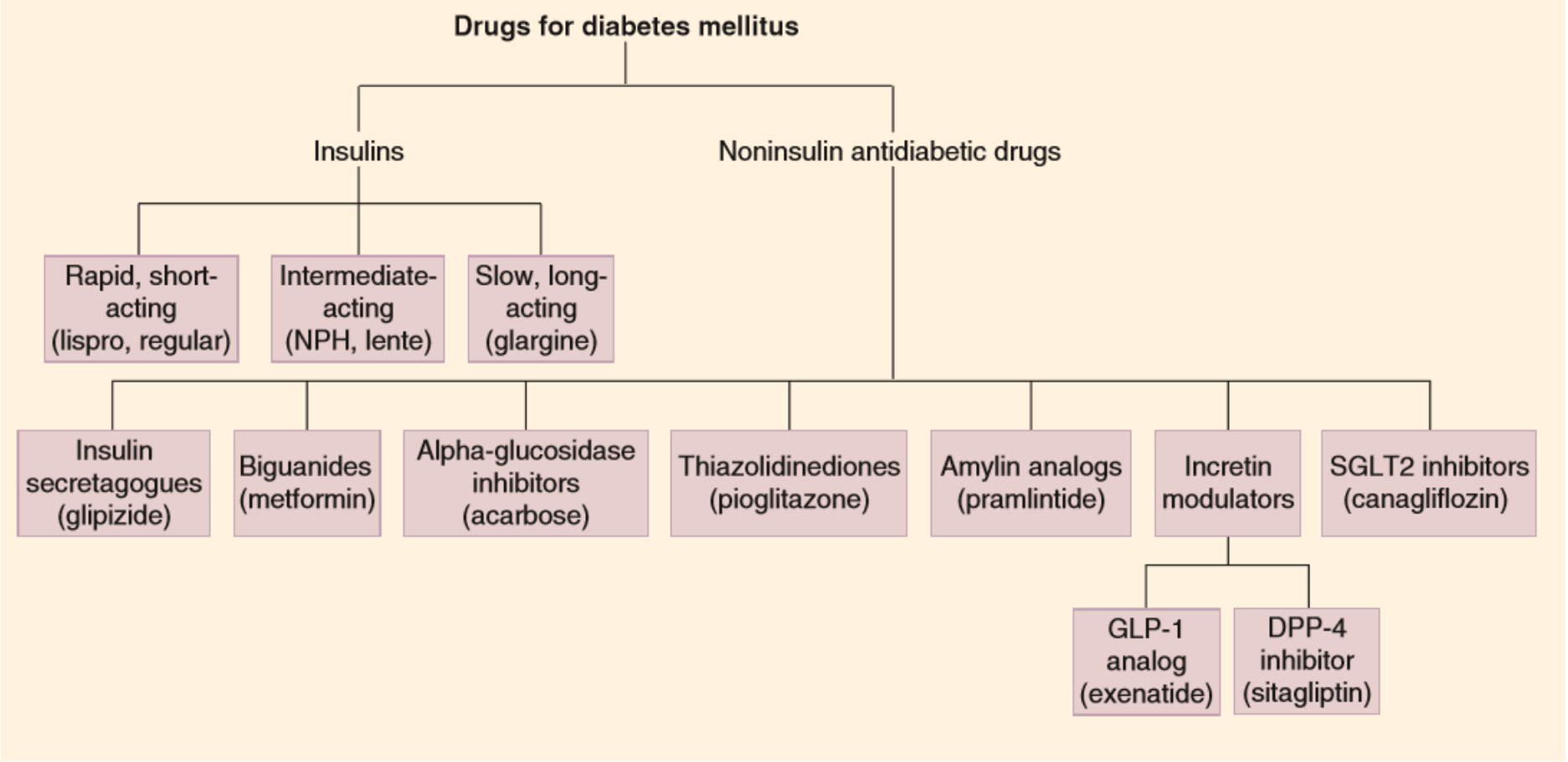
❖ Types of D.M.:

Primary		Secondary to other diseases
Type I (Insulin Dependent Diabetes Mellitus) (IDDM)	**Type II (Non-Insulin Dépendent Diabètes Mellites) (NIDDM)**	**-Diseases** of pancreas (chronic pancreatitis) or after pancreatectomy **Drugs**: inhibitors of insulin secretion: B blockers , α2 agonists ,calcium & sodium channel blockers ,loop and thiazide diuretics (k loss), K channel openers, Counter-regulating hormones :glucagon, growth hormone, glucocorticoids, thyroxin, and catecholamines Cytotoxic drugs that destroy B-cells as streptozotocin and alloxan
Absolute insulin deficiency due to B cell destruction or immune mediated	relative insulin deficiency or a defect in the biological effect of insulin (insensitivity)	
young age (< 30 years), NON-Obese	older patients (> 40 years), Obese	
Treated by insulin	- Non complicated cases are treated by oral hypoglycemic drugs - resistant and complicated cases need insulin	
diabetic ketoacidosis (DKA) is common	Ketoacidosis is rare	

-Gestational diabetes due to excess anti-insulin hormones is classified as type III diabetes

Diabetes mellitus

❑ Anti-Diabetic Drugs



Diabetes mellitus

❑ Insulin:

❑ Synthetic insulin produced from:

- **Animal pancreatic extracts insulin**: from Bovine and Porcine pancreas, → more antigenic and can cause insulin resistance.
- **Human insulin**: by recombinant DNA technology (genetic engineering), → Less antigenic and rare development of insulin resistance e.g. regular insulin, neutral protamine hagedorn (NPH) insulin,
- **Human insulin analogs**: Recombinant insulin analogs alteration of amino acid sequence of human insulin" → different pharmacokinetic properties.as:
  - Rapidly acting insulin analogues e.g. insulin lispro, insulin aspart and insulin glulisine.
  - Long-acting insulin analogues, e.g. insulin glargine and insulin detemir.

❖ Pharmacokinetics

- Not given orally due to destroyed by proteolytic enzymes in the gut.
- All insulin given by SC injection in all type I patients.
- Only regular (soluble) insulin is given IV (in emergencies) and SC.
- Insulin is distributed to all tissues.
- insulin is metabolized by glutathione insulin transhydrogenase (insulinase) in liver and kidney which breaks the disulphide links, then the polypeptide chains are degraded by polypeptidases.

Diabetes mellitus

❖ Insulin Preparations:

1. **Rapid acting insulin analogs (Ultrashort acting): rapid onset+ short duration.** :
EX: Insulin lispro, Insulin aspart ,Insulin glulisine
- Rapid onset of action (5–15 min;) → given SC 15 minutes before meals
– short duration of action is about 4 h; → lower risk of late postprandial hypoglycemia.

2- **Short-acting insulin**: slower onset (30 min) + longer duration (5-8 h) than ultra-short
EX: Regular insulin or Crystalline Zinc
- Soluble neutral crystalline zinc insulin.
- Short-acting insulin can be given SC, 30-45min before meals
- Used IV in emergencies: ketoacidosis.

3- **Intermediate-acting insulin**:

- Isophan insulin = Neutral Protamine Hagedorn (NPH)
- Contains balanced amounts of Insulin, Zn & protamine → onset of action is delayed (1-2 h) and duration of action is 10–20 h.

- Pre-mixed insulin: (Mixtard)®
- Mixture of 30% regular insulin + 70% NPH insulin → rapid onset of action (30 min) and sustained action (24 hours).
- Useful as SC in all forms of diabetes except ketoacidosis. (basal &postprandial in type I & type II)

4- **Prolonged acting insulin**: Insulin glargine, Insulin detemir

- Slow onset (1-4 h), long acting (18-24h), given once daily.
- Cannot be mixed in the same syringe with other insulins because of its acidic pH.
- used for basal control (better controlled than NPH insulin).

❖ Indications for insulin

1- **Diabetic indications:**

- Type I (IDDM).
- Diabetic Keto-Acidosis (DKA) by regular soluble insulin IV.
- Temporarily in Type II (NIDDM) in cases of "stress" due to: infections – surgery pregnancy –lactation- trauma.
- Permanently in Type II (NIDDM) in cases of:
  - Failure to control hyperglycemia by diet+ exercise + oral anti-diabetics.
  - Development of renal or hepatic impairment.

2- **Treatment of hyperkalemia** due to renal impairment. Insulin enhances k+ influx in to cells.

Diabetes mellitus

❖ Adverse effects:

- **Hypoglycemia**: Most frequent and most serious-→ brain damage
  - Causes: excessive dose of insulin, insufficient food , excessive exercise or diarrhea
  - Manifested by headache, anxiety, confusion, tachycardia & tremors. → coma and it is more serious than hyperglycemic coma
  - Treatment: If the patient is conscious: oral glucose or sweets (candy, juice, chocolate).
    patient is comatose: IV glucose or glucagon1mg IM or SC.

- **Lipodystrophy**: Due to repeated injection at same site- prevented by changing the site of injection regularly

- **Allergic reactions** are rare; local skin reactions (swelling, redness) at the site of injection

- **Insulin resistance** (daily insulin requirements exceed 200 Units, common in obese non exercising patients, and may improve by adding insulin sensitizers as metformin or glitazones)

- **Hypokalemia** may occur especially with IV insulin therapy in DKA.

- **Weight gain** due to salt and water retention (antidiuretic effect)

Diabetes mellitus

❑ Diabetic ketoacidosis.

- Diabetic ketoacidosis is a complication of Type 1 diabetes mellitus.
- It is very rare in Type 2 DM.
- The common precipitating factors are infection, trauma, severe stress, etc.
- The clinical features are anorexia, nausea, vomiting, polyuria, abdominal pain, hypotension, tachycardia, hyperventilation, altered consciousness or coma in untreated cases.
- It is treated with regular insulin (i.v.); correction of fluid and electrolyte imbalance is essentia

❖ Drug interactions

- **Salicylates insulin**: Salicylates exert hypoglycaemic effect by increasing the sensitivity of pancreatic B-cells to glucose and potentiating insulin secretion

❖ Methods of Administration:

1- Disposable plastic syringes.
2- Insulin pen (more accurate dosage and less painful).
3- Insulin pump.

Diabetes mellitus

- **Oral anti-diabetic drugs**: given orally for type II D.M.

I. Insulin Secretagogues: stimulate insulin release from B-cells → known as oral hypoglycemics drugs)
- Sulfonylureas: e.g. glimepiride
- Non-sulfonylureas: e.g. repaglinide

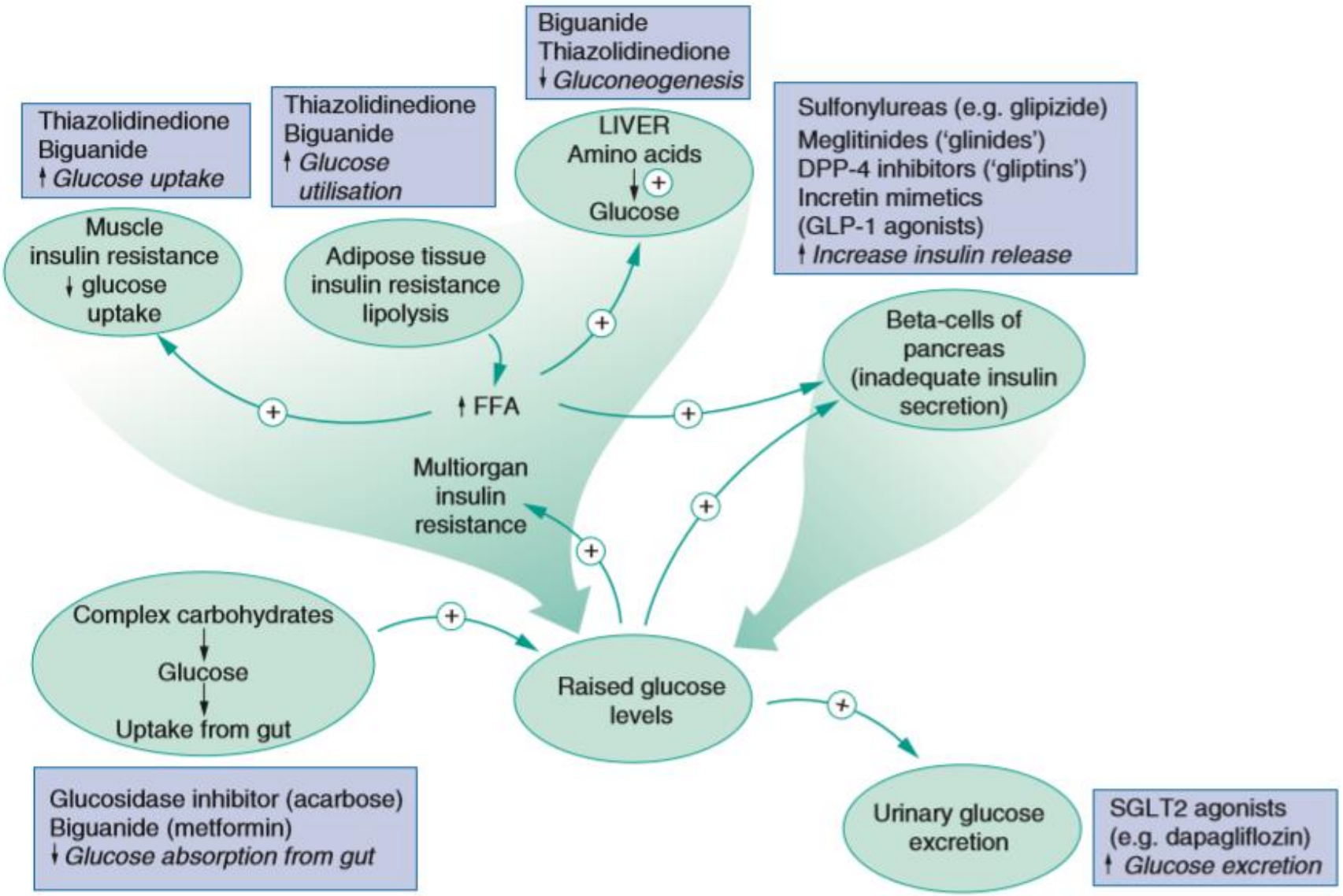
II. **Insulin Sensitizers:** improve the action of insulin on insulin receptors. → never induce hypoglycemic → known as oral euglycemic".
- Biguanides: e.g. metformin
- Thiazolidinediones(Tzd): pioglitazone

III .**α-glucosidase Inhibitors:** inhibit a-glucosidase enzymes in the intestinal mucosa → inhibition digestion of dietary carbohydrates into glucose. e.g.: acarbose

IV. **Dipeptidylpeptidase-4(DPP-4) Inhibitor**s: incretin enhancers e.g. sitagliptin

V. **Other antidiabetics (SC)**
- Incretin mimetics (e.g. exenatide.),
- Amylin analogues (e.g. pramlintide)

Diabetes mellitus



Diabetes mellitus

I-Insulin secretagogues (oral hypoglycemics drugs) **:**

1. **Sulfonylureas (SU):**
   - **First generation SU**: as Tolbutamide, chlorpropamide,
   Less frequently used due to adverse effects & drug interactions.

- **Second generation SU**. More potent, Less adverse effects & interactions. long acting (12-24 h.) as Glibenclamide (Glyburide)- Glipizide- Gliclazide- Glimepiride (most potent).

- sulphonamide derivatives, may cause severe allergic reactions, → acute myocardial infarction causing sudden death

❖ Mechanism of action:

- Stimulation of insulin release from βcells by blocking ATP-sensitive K+ channel → depolarization → ↑ Ca+2 influx. (insulin secretagogues)
- ↓ Serum glucagon level.
- ↑ Peripheral insulin sensitivity.
- Given orally once or twice daily.
- Bound to plasma proteins, Metabolized in liver.
- Excreted in liver and kidney. (avoided in hepatic or renal impairment → hypoglycemia)
- Cross placenta. (Contraindicated during pregnancy → deplete insulin from fetal pancreas)

Diabetes mellitus

❖ Indications:

- Type 2 DM: If initial therapy with metformin + diet control + exercise fail or if Metformin is contraindicated

❖ Side effects:

- **Hypoglycemia**: more with drugs as glibenclamide particularly e.g. in elderly, renal or liver disease.
- ↑**Appetite**: Weight gain.
- **GIT disturbances**: like nausea, vomiting, diarrhoea and flatulence. .
- **Allergic reactions**: drug allergy as skin rash. (To sulfa compounds).
- **Teratogenicity**: Sulfonylureas are not safe during pregnancy

❖ Contraindications of Sulfonylureas

- DM with pregnancy & lactation
- DM with stress, e.g. infection, surgery, trauma or myocardial infarction .
- DM with liver or renal disease →↑ risk of hypoglycemia

❖ Drug interactions

- salicylates/sulphonamides: → displace sulfonylureas from the plasma protein-binding site → severe hypoglycemia).
- Allopurinol, MAO inhibitors & chloramphenicol → ↓ metabolism.
- Thiazide, corticosteroids & sympathomimetics → ↓ efficacy.

2. **Non-sulfonylureas:**

❑ **Meglitinides**: as Repaglinide and Nateglinide.

- Increase insulin secretion as sulfonylureas with less side effects.
- Rapid onset and short duration (about 2 hours) → taken orally just before meals to control postprandial hyperglycemia.
- Used only in type-2 DM to control postprandial hyperglycaemia.
- Usually used in combination with metformin or glitazones.
- Don't contain sulfur, so they can be used in patients allergic to sulfonylureas.
- **The side effect**: weight gain and hypoglycaemia (less than sulfonylureas)
- They should be used with caution in patients with hepatic impairment

II. **Insulin Sensitizers** (oral euglycemic)

A. **Biguanides**: as metformin (Glucophage)® 500-850 mg bid or tid

❖ **Mechanism of action:**

- ↑ Peripheral glucose utilization → ↓ insulin resistance. (insulin sensitizers)
- ↓ Glucose absorption from GIT. ↓ Hepatic gluconeogenesis. → It does not increase insulin secretion (so they are not affecting normal blood glucose level, doesn't cause hypoglycemia).
- ↓ Hyperlipidemia & suppress appetite (↓ glucose absorption)..

- Well absorbed orally and not bound to plasma proteins.
- No hypoglycemia , no salt & water retention

❖ Therapeutic uses

- first-line drug for the treatment of type 2 DM especially in obese patients. as alone or in combination with other antidiabetic agents.
- Treatment of polycystic ovary syndrome (POS); by reducing obesity which reduces peripheral conversion of estrogen to androgen by adipose tissue and restores normal menstrual cycles.

❖ Adverse effects:

- GIT upset (the most common): anorexia, vomiting, and diarrhea. -
- Megaloblastic anemia (↓Vitamin B12 absorption)
- Lactic acidosis: due to increased anaerobic glycolysis:.

❖ **Contraindications of Metformin:** in renal failure, liver failure & severe hypoxia (as HF, MI, pneumonia and alcoholics) due to ↑ risk of lactic acidosis (anaerobic metabolism) in these patients.

B. Thiazolidinediones (TZDs): Pioglitazone (Actos)®

- Insulin sensitizers.
- They act on nuclear genes called peroxisome proliferator-activated receptor gamma (PPAR-γ) present in muscles, adipose tissue, and liver cells leading to:
  - ↑ insulin receptor sensitivity and ↓ insulin resistance.
  - ↑ number of glucose transporters →↑ glucose uptake.
  - They have beneficial effect on serum lipoprotein levels (Hypolipidemic effect, ↓TGs).

- **Used** as monotherapy or in combination in type2DM. (If metformin & sulfonylurea are contraindicated).
- Given once daily (t½ = 24 hours)

❖ **Adverse effects**

- Hepatotoxicity is rare
- Fluid retention leading to peripheral edema & weight gain. (They should be avoided in patients with CHF).

- **Contraindicated:** pregnancy- liver impairment-hypertension and heart failure

Diabetes mellitus

III .**α-glucosidase Inhibitors: as** Acarbose

- ↓ Glucosidase enzyme in the intestine → ↓ absorption of starch and monosaccharides → ↓ blood glucose. → ↓ postprandial hyperglycaemia
- Do not cause hypoglycemia
- used to control Post-Prandial hyperglycemia in type II DM, can be given with sulfonylurea but not with metformin.
- Taken before meals.
- **Side effects**: flatulence, diarrhea & abdominal pain.

NB:

- **Incretins** are group of metabolic hormones peptides released by gastric and intestinal cells after eating to stimulate insulin secretion and lower plasma glucose.
- They are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4).
- The most important incretin peptide is glucagon-like peptide-1 (GLP-1).

Diabetes mellitus

IV. Dipeptidylpeptidase-4(DPP-4) Inhibitors: incretin enhancers e.g. sitagliptin

- They inhibit dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for the proteolysis of the incretin GLP-1 → prolong the activity of incretin hormones → ↑ insulin release and ↓ glucagon secretion, slows gastric emptying → ↓ post prandial hyperglycemia
- Given orally once daily and excreted with urine.
- **Used** alone or with metformin and pioglitazone for Type 2 DM .
- **Side effects**: Headache, nausea and pancreatitis

V. Incretin mimetics: As exenatide S.C. injection twice/day

- Glucagon-like peptide-1 (GLP-1) agonist → improves glucose-dependent insulin secretion
- Also slows gastric emptying time, ↓ food intake &↓ appetite → ↓ postprandial glucagon secretion.
- Given S.C as adjuvant therapy with sulfonylureas or glitazones for treatment of type2 diabetes.

- **Side effects**: nausea, vomiting and diarrhea.

Diabetes mellitus

VI. Amylin analogs: As pramlintide

- Synthetic analog of amylin hormone (secretes from β-cells along with insulin) which suppresses glucagon release, slows gastric emptying and reduces appetite.
- Given S.C with insulin in type I and type II D.M to prevent post-prandial hyperglycemia

- **Side effects**: GIT upset and hypoglycemia.

Diabetes mellitus

Non-pharmacological therapy: (Life style modifications)

- Moderate exercise.
- Weight reduction.
- Diet balance by decreasing carbohydrate, fat and proteins intake.

Management of type-1 diabetes mellitus:

- S.C insulin (usually intermediate or long-acting insulin)
- Life style modifications.
- Maintain blood glucose concentration as close to normal as possible.
- Turn to regular insulin in case of infection or during surgery.

Management of type-2 diabetes mellitus:

- Start by life style modifications.
- Use oral hypoglycemic drugs:
- Metformin especially in obese patients.
- Add sulfonylureas + metformin.
- Add other adjuvant therapy in cases of resistance.

- ❑ Maintain blood glucose concentration within normal limits.
- ❑ If no response or in infections, surgery or pregnancy, stop oral therapy and give SC insulin.

Diabetes mellitus

Management of diabetic ketoacidosis: (DKA)

- NaCl 0.9% by infusion.
- IV infusion of regular insulin (0.1 unit/kg/h)
- IV infusion of sodium bicarbonate to control acidosis.
- After patient is stable, turn to S.C insulin (long acting) and add dextrose 5% to NaCl.
- Monitor potassium level to prevent hypokalemia.

Drugs affecting the endocrine system (Hormones)

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Adrenocortical Hormones (Corticosteroids)

Adrenocortical Hormones (Corticosteroids)

- The adrenal gland (cortex) synthesizes and secretes the following hormones:
  - **Glucocorticosteroids**: as cortisol (hydrocortisone).
  - **Mineralocorticosteroids**: as aldosterone
  - **Sex hormones:** estrogens and androgens are secreted in small amounts.

Layers of Adrenal Cortex	Zona Glomerulosa	Zona Fasciculata
Hormones secreted	Mineralocorticoids: Aldosterone Desoxycorticosterone	Glucocorticoids: Hydrocortisone (cortisol)
Main actions	Regulate water and electrolyte balance	Metabolic (carbohydrate, protein and fat), antiinflammatory, immunosuppressant and antiallergic actions
Hypersecretion	Primary hyperaldosteronism (Conn's syndrome)	Cushing's syndrome
Deficiency of adrenal cortical hormones (chronic)	← Addison's disease	

Adrenocortical Hormones (Corticosteroids)

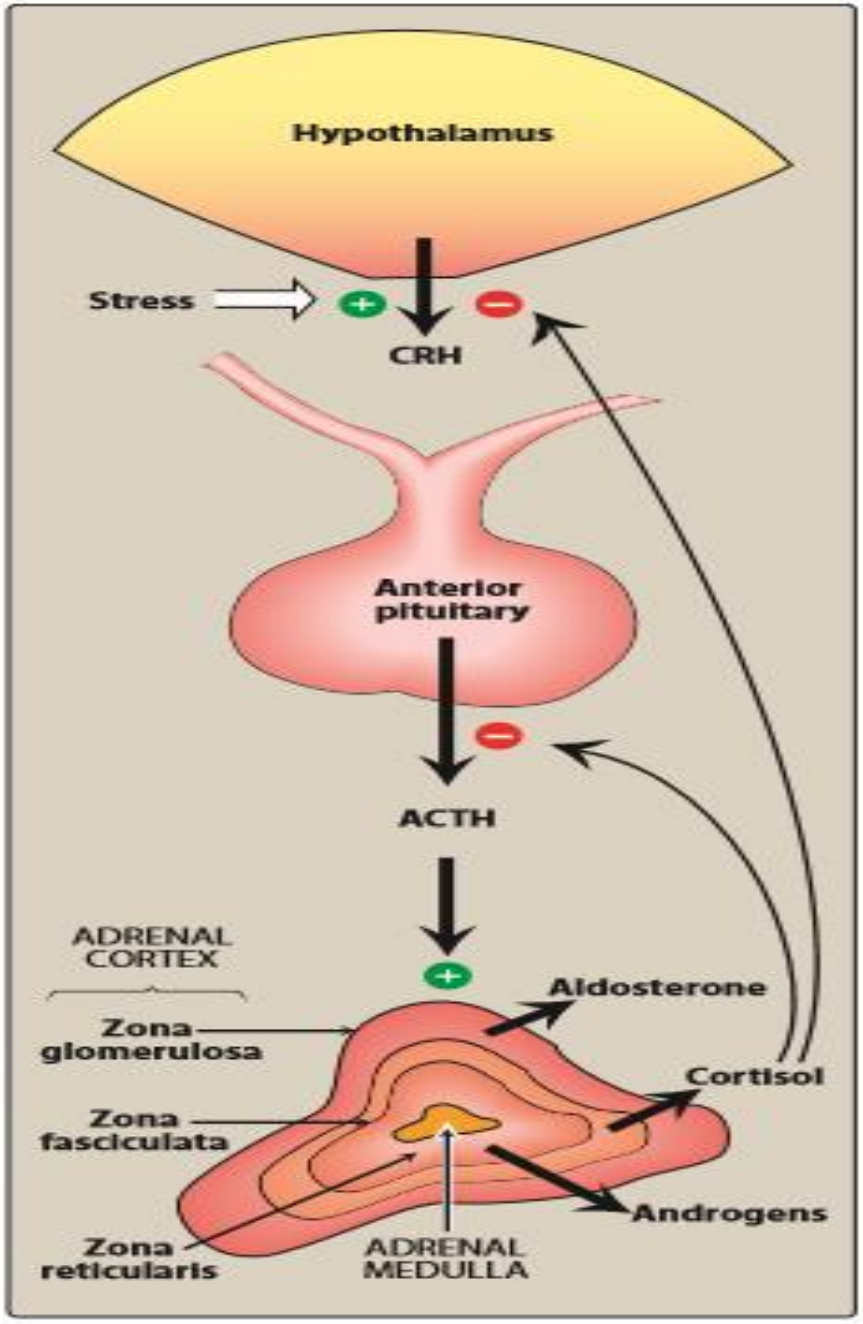
- Secretion is controlled by pituitary adrenocorticotropic hormone [ACTH or corticotropin], which is released in response to the hypothalamic corticotropin-releasing hormone (CRH).

- Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion

- **Stimulated by:**
  1. Stress (infection, surgery, trauma, and pregnancy).
  2. Day-light
  3. Low plasma cortisol level.

- **Inhibited by:**
  1. Negative feedback effect of cortisol.
  2. Night.

- Mineralocorticoid (e.g. aldosterone) release is controlled by the renin–angiotensin system



Adrenocortical Hormones (Corticosteroids)

❑ Glucocorticoids:

❖ Mechanism of Action

- Bind with steroid receptor in cytoplasmic → the complex enters into the nucleus → nuclear receptors (a specific site on DNA strands):
  - **Gene expression**: → synthesis of specific proteins as Lipocortin I and catabolic enzymes.
  - **Gene repression**: inhibition of synthesis of certain proteins as COX-II, Inflammatory mediators and antibodies (immunoglobulins).

❖ Pharmacological actions:

1. **On carbohydrate**: ↓ glucose utilization & ↑ gluconeogenesis → Hyperglycemia and diabetes mellitus.
2. **On proteins:** catabolic on skin, muscles and lymphoid tissues →. Muscle wasting, thin arms & legs, Retardation of growth (children), Osteoporosis (↓ protein &Ca2+) and delayed wound healing.
3. **On fats:** ↑ lipolysis and redistribute fats to face, shoulder and abdomen →Moon face, ↑ abdominal fat, Buffalo hump, obesity.
4. **Weak Sodium retention and potassium excretion**. → oedema and hypertension Hypokalemic alkalosis
5. ↑ Uric acid excretion.

Adrenocortical Hormones (Corticosteroids)

6. **Antagonize vitamin D**, ↓ calcium absorption → osteoporosis.
7. **On CNS**: euphoria & psychosis.
8. ↑ **Gastric acid & pepsin** and ↓ mucous secretion.
9. ↑ **RBCs, platelets** & neutrophils and ↓ eosinophils and lymphocytes.

10. Anti-inflammatory effect: powerful antiinflammatory.
- Due to inhibition of phospholipase activity → ↓ arachidonic acid synthesis → ↓ synthesis of prostaglandins and leukotrienes.
- Also, they ↓ leucocyte & macrophage activity and interference with mast cell degranulation (↓ histamine and capillary permeability)
- it masks the signs of infection and inflammation without treating the cause.

11. **Inhibit antigen/antibody reaction**. (anti-allergic & immunosuppressant action)

12. Stabilization of the membrane of mast cells to prevent the release of allegro toxins in bronchial asthma (↑ number of B2-receptors)

13. ↑ Resistance to stress and shock reaction. (by ↑ glucose level, blood volume and BP)

Adrenocortical Hormones (Corticosteroids)

Agent	Activity		Equivalent dose (mg) (Antiinflammatory)	Uses and route of administration
	Antiinflammatory	Salt retaining		
1. Glucocorticoids				
(a) **Short acting** (8–12 hours)				
(i) Hydrocortisone (cortisol)	1	1	20	It has a rapid onset but short duration of action. It is the drug of choice for replacement therapy in acute adrenal insufficiency. Other uses are status asthmaticus and anaphylactic shock (emergency uses) *Routes*: Oral, i.m., i.v., intra-articular and topical
(ii) Cortisone	0.8	0.8	25	It is cheap; prodrug, converted to hydrocortisone after metabolism in liver; rarely used at present
(b) **Intermediate acting** (12–36 hours)				
(i) Prednisolone	4	0.8	5	It is the most commonly used preparation for allergic, inflammatory, autoimmune disorders and in malignancies. It causes less HPA axis suppression if given once daily in the morning *Routes*: Oral, i.m., intra-articular and topical
(ii) Prednisone	4	0.8	5	It is a prodrug, gets converted to prednisolone in liver; less efficacious, hence rarely used
(iii) Methyl-prednisolone	5	0.5	4	It is used for its antiinflammatory and immunosuppressant effects; as high-dose pulse therapy in renal transplant, pemphigus vulgaris, etc. *Routes*: i.m., i.v., retention enema in ulcerative colitis
(iv) Tri**am**cinolone*	5	0	4	More potent and relatively more toxic than prednisolone. It has **no mineralocorticoid activity** *Routes*: Oral, i.m., intra-articular and topical

Adrenocortical Hormones (Corticosteroids)

Agent	Activity		Equivalent dose (mg) (Antiinflammatory)	Uses and route of administration
	Antiinflammatory	Salt retaining		
(c) **Long acting** (36–72 hours)				Long acting; have highly potent antiinflammatory and immunosuppressant effects. Have **no mineralocorticoid activity**
(i) Bet**am**ethasone*	30	0	0.75	They cause severe HPA axis suppression. Used in allergic and inflammatory conditions; cerebral oedema due to neoplasm, where water retention is undesirable and to promote lung maturation in fetus when premature delivery is anticipated
(ii) Dex**am**ethasone*	30	0	0.75	*Routes:* Oral, i.v., i.m. and topical
Local acting glucocorticoids				They have local action
(i) Beclomethasone	+	–	–	It is used by inhalation in bronchial asthma, as nasal spray for allergic rhinitis; as ointment for skin and mucous membrane lesions. HPA-axis suppression is minimal
(ii) Budesonide	+	–	–	Same as beclomethasone, but is more potent than beclomethasone
(iii) Fluticasone	+	–	–	It is used by inhalation for asthma and chronic obstructive pulmonary disease (COPD); orally for inflammatory bowel disease; as ointment for skin and mucous membrane lesions
2. Mineralocorticoids				
(i) Desoxycortico-sterone acetate (DOCA)	0	100	–	It has selective mineralocorticoid activity and is used in Addison's disease as replacement therapy
(ii) Fludrocortisone	10	125	2	Has potent mineralocorticoid activity. It is used with hydrocortisone for replacement therapy in Addison's disease
(iii) Aldosterone	0.3	3000	–	Not used

Adrenocortical Hormones (Corticosteroids)

❖ Pharmacokinetics:

- Given orally, parenterally, topically, intra-articularly, an aerosol for either oral or intranasal inhalation.
- bound to plasma proteins. Pass BBB. • Pass placental → teratogenicity.
- Metabolized by the liver microsomal enzymes (conjugated to glucuronic acid or sulfate)
- Given in caution with hepatic and renal dysfunction.

❖ Examples of drugs:

- Hydrocortisone. (Hydrocortisone)®
- Prednisolone (Prednisone)®
- Methyl prednisolone (Depo-Medrol)®
- Triamcinolone. (Kenacort)®
- Betamethasone. (Diprofos)®
- Dexamethasone. (Decadron)®

Adrenocortical Hormones (Corticosteroids)

❖ Therapeutic uses

A-Replacement Therapy:

1. Acute adrenocortical insufficiency (acute Addisonian crisis)
   - Saline & 5%glucose → maintain fluid & salt balance & blood sugar.
   - .IV hydrocortisone.

2. Chronic adrenocortical insufficiency (chronic Addison's disease):
   - Oral hydrocortisone: dose is ↑ during stress or surgery.
   - Fludrocortisone (orally): maintains Na+ balance & BP.

B. **Anti-allergic:**
- Bronchial asthma
- Allergic conditions: skin, eye, GIT. and anaphylactic shock

c. **Immunosuppressants in:**
- Autoimmune diseases: rheumatoid arthritis.
- Organ transplantation.

d. **In acute edema** as cerebral or pulmonary edema.
e. **In some blood diseases** as lymphocytic leukemia and hemolytic anemia.
f. **Hypercalcemia and hypervitaminosis** D (vitamin D intoxication).

Adrenocortical Hormones (Corticosteroids)

❖ Side effects of long term therapy:

- ❑ The risk for side effects depends both on dose and duration of therapy.
- ❑ Topical and inhaled corticosteroids are less side effects than oral or parenteral forms.

1. Hypertension. Hyperglycemia. Hypokalemia, Osteoporosis.
2. Hirsutism and menstrual disturbances
3. Cushing-like syndrome. (moon face, redistribution of body fat, ↑ hair growth, acne, insomnia and ↑ appetite)
4. Euphoria and psychosis. (elevation of mood)
5. Peptic ulcer.
6. ↑ Risk of infection. (immune-suppressive action)

❖ Contraindications

- ➢ Sudden withdrawal of glucocorticoids after prolonged use.
- ➢ Cushing syndrome. - Peptic ulcer. . - Pregnancy.
- ➢ Diabetes mellitus. - Osteoporosis.
- ➢ Hypertension. - CHF. - Glaucoma.
- ➢ In digitalis toxicity and with K+ losing diuretics.
- ➢ Uncontrolled infections.
- ➢ Thrombo-embolic diseases.
- ➢ Psychotic patients

Adrenocortical Hormones (Corticosteroids)

❖ Drugs that inhibit adrenocortical steroids:

- Ketoconazole: antifungal used in Cushing disease (inhibits adrenal steroid synthesis).
- Spironolactone :aldosterone antagonist used in hyper-aldosteronism, heart failure, hypertension & in hirsutism in women (blocks androgen receptor in hair follicle).
- ➢ Metyrapone: Inhibits steroid II-β-hydroxylase enzyme → blocks cortisol synthesis. (used in treatment of Cushing syndrome)
- Mifepristone: blocks corticosteroid receptors at high doses.

Sex hormones

Sex hormones

- The gonadal hormones (Sex hormones) include :
  - in Ovary (estrogens and progestogens)
  - in Testis (Androgens (testosterone).

- They are produced under the effects of Gonadotropin-releasing hormone (GnRH) from hypothalamus and Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) from pituitary.

- **FSH:** - In Females → Ripening of Ovarian follicle + Synthesis & release of Estradiol (estrogen). Useful in treatment of Infertility.
  - ln Males → F.S.H. +Testosterone → Spermatogenesis → Fertility. (treatment of Infertility)
- **LH:**- In Females → Complete the maturation of ovarian follicle, ovulation & maintain Corpus luteum → secrete Estradiol & Progesterone (treatment of Infertility)
- In Males → Testosterone secretion → Puberty (treatment of Delayed puberty)

- All sex hormones are synthesized from cholesterol.

Sex hormones

❑ Estrogens:

- **Natural estrogens**: Estradiol (The most potent estrogen).
  - Ineffective orally due to extensive first pass effect.

- **Synthetic estrogens**: Ethinyl estradiol, mestranol (Steroidal)
  - Diethylstilbesterol (Non-Steroidal).
  - Effective orally (less first pass effect).

❖ Pharmacokinetics:

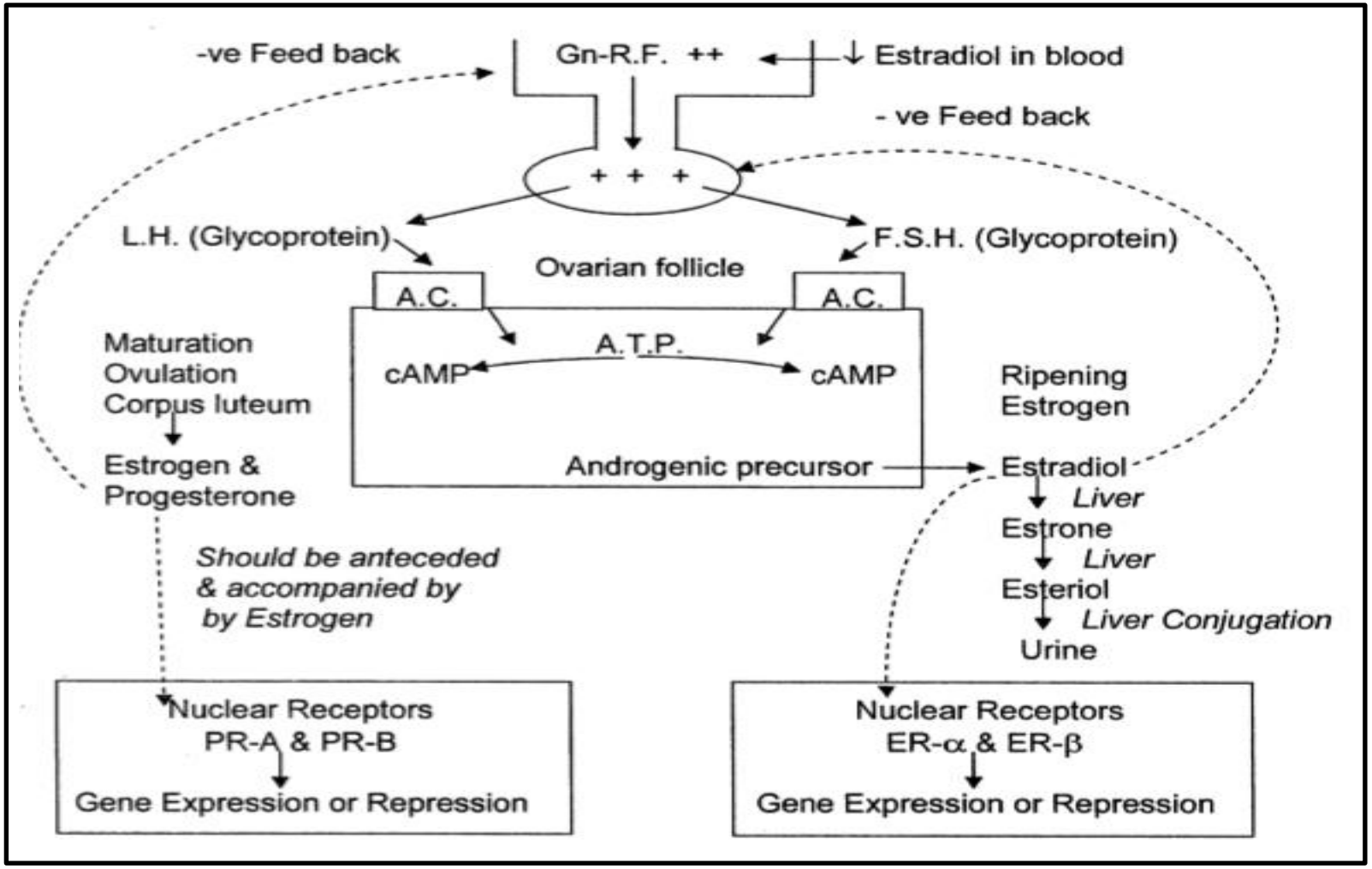
- Estradiol is given by IM injection, topically & Transdermal patch.
- Synthetic estrogens have a prolonged action and a higher potency compared to natural estrogens.

❖ Mechanism of action:

- Bind with Nuclear Estrogen Receptors (ER-a & ER-b) →Gene expression or Repression that mediate a number of physiologic functions
- ER-a stimulates gene transcription whereas ER-b inhibits transcription.

Sex hormones

- Control of secretion of female sex hormones



Estrogen	**Progesterone**
▪ Small (physiological) doses : ↑ secretion of FSH and LH ▪ Intermediate (physiological dose): Stimulates LH and inhibits FSH and induce ovulation ▪ Large pharmacological dose & Exogenous Estrogen : inhibits FSH &LH & ovulation (contraceptive pills) ▪ In male: inhibits FSH &LH & Testosterone	▪ Inhibits FSH &LH and ovulation (contraceptive pills)
▪ Small dose ↑ angiotensinogen ,α receptors synthesis (hypertension)	▪ Hypertension due to metabolism to mineralocorticoid like metabolites
▪ Small dose: ↑ prolactin receptors &lactation ▪ Large dose: decrease prolactin secretion, Inhibits lactation	▪ Increase prolactin release and milk synthesis
▪ Increases bone density by vitamin D activation	▪ Promotes calcitonin & decrease bone density.
▪ Insulin resistance → hyperglycemia due to increase release of insulin antagonists eg growth hormone	
▪ Increase biliary removal of cholesterol from plasma by stimulation of LDL receptors	▪ Increase cholesterol ,LDL due to insulin resistance
▪ Induce oxytocin receptors :increase uterine contraction (facilitate transport of sperm &labor& menstruation.	▪ Decrease oxytocin & estrogen receptors ,uterine relaxation

Effect of female sex hormone on female sex organs

Estrogen: Prepares female body for pregnancy	Progesterone: pregnancy maintaining hormone
Endometrium : cell proliferation &growth	Endometrium : formation of secretory phase (Help implantation of fertilized ovum)
Increase contraction of uterus & uterine tube	Relaxation of uterus and uterine tube
Cervix: Watery secretion from cervix (promote sperm transport)	Cervix: Thick mucous plug (Contraceptive).

Mild anabolic for female body proteins (skin , bone , muscles	Catabolic for mother to transport nutrients to fetus
CNS: Cognitive & mood stimulant due to increase 5HT synthesis	Sedative and mood depressant due to increase GABA synthesis
Increase clotting factors (promote thrombosis &melanin pigment(cloasma)	No effect
Carcinogenic: Promotes cancer uterus and breast. It promotes vaginal adenosis in female fetus if taken by the mother during pregnancy	Inhibit cancer uterus , breast ,augment the effect of anticancer drugs by prevention of their efflux

Sex hormones

❖ Therapeutic uses of Estrogens:

- **Hormonal Replacement therapy** in:
  - Primary hypogonadism. Delayed puberty (more than 17 years).
  - ↓ Menopausal syndrome (osteoporosis, hot flushes, to elevate the mood , vaginal dryness and hyperlipidemia causing atherosclerosis and ischemic heart diseases.
- **Oral Contraception alone or combination with progesterone**.
- **Suppression of lactation** ((weaning).
- In males to suppress androgen dependent cancer prostate.

❖ Adverse effects of Estrogens :

- Nausea and breast tenderness and weight gain. (Salt & water retention).
- ↑ Risk of thromboembolism, myocardial infarction and (Occur with high doses and long duration but lesser with adding progesterone)
- ↑ Risk of breast &uterus &vagina (endometrial) cancer.
- In male: feminization- impotence -↓ libido- gynecomastia
- Estrogens antagonize the action of: anticoagulants, diuretics, antihypertensives and antidiabetics.

Sex hormones

❖ Selective Estrogen Receptor Modulators: (SERMs)

- SERMs are non-steroidal estrogen-related compounds
- Mixed agonists/antagonist estrogenic effects that have agonist activity in one tissue but antagonist activity or no activity in another tissue.

- Preparation : clomiphene, Tamoxifen, raloxifene

Drug	Action	Therapeutic uses
Clomiphene	▪ **Estrogen antagonist**: hypothalamus → ↑ FSH & LH →An ovulation-inducing agent. ▪ **Estrogen agonist**: Uterus & blood	-(oral) Induction of ovulation for infertility
Tamoxifin Toremifene	▪ **Estrogen antagonist** : breast ▪ **Agonist** : uterus and bone	Treatment of breast cancer
Raloxifene	▪ **Estrogen antagonist**: breast and uterus ▪ **Estrogen agonist**: bone	Treatment of cancer breast & uterus & osteoporosis (in postmenopausal women)

- **Side effects:**

- Nausea, visual disturbances and hot flashes
- ↑ Risk of thromboembolism, multiple ovulations and multiple twins (Clomiphene).
- ↑ Risk of cancer uterus due to estrogen like action on uterus (tamoxifen).

Sex hormones

❑ Progestogens

- The natural progestogen is produced in response to LH by both females and by males, also synthesized by the adrenal cortex.

➢ **Natural**: Progesterone injection, Not effective orally (first pass metabolism).

➢

➢ **Synthetic**: Norethindrone- Norgestrel- medroxyprogesterone, levonorgestrel
- Effective orally, Long duration of action.

❖ Therapeutic uses

- Contraceptive pills: alone or combined with estrogen.
- Maintain pregnancy, Threatened abortion (Use progesterone derivatives).
- Estrogen dependent cancer body of uterus
- Treatment of dysmenorrhea and management of endometriosis.

❖ Adverse effects

- Sodium and water retention. Edema- hypertension- weight gain
- Acne and hirsutism in some progestins that have structural similarity to testosterone (androgenic effect) (norethindrone, norgestrel, levonorgestrel)
- Psychic depression.
- Elevation of LDL-cholesterol and atherosclerosis.

❑ Anti-Progesterones:

1. Mifepristone

- It is a competitive blocker of progesterone receptors and glucocorticoid receptors.
- Given early in pregnancy → ↑ uterine contractions → abortion of the fetus
- It is used + prostaglandin E2 analogue (misoprostol) to induction of abortion in the first trimester. Also used in Cushing syndrome.
- **Adverse effects** are uterine bleeding and the possibility of an incomplete abortion.

Sex hormones

❑ Contraceptives

1-Hormonal Contraceptives: orally, IM, or by S.C. implantation.

A. Oral Preparations

1. Combined Preparations

- Combined preparations (the most effective type)
- Contain both estrogen (ethinyl estradiol) + progesterone (norethindrone, levonorgestrel) given from the 5th day of menstruation for 21 days. then rest for 7 days or take placebo during this week to allow menstruation.

- **Monophasic** combination pills contain a constant dose of estrogen and progestin.
- **Biphasic and triphasic** oral contraceptives contain a constant dose of estrogen with increasing doses of progestin to mimic the natural female cycle.

- **Advantages**: Most effective, Lower amounts of hormones, Similar to the natural menstrual cycle.

2. Progestin-Only Preparations (Minipills)

- Pills contain progestogen only (norethindrone or levonorgestrel).
- Used in breast-feeding (no effect on milk production).
- less effective than combined method.

3. Post-Coital Pills (Emergency Pills =Morning after = Rape pills):

- Estrogen only (diethylstilbestrol) is given within 72 hours after coitus (sexual intercourse) and for 5 days.
- Estrogen + progestogen given twice (every 12 hours) within 72 hours after intercourse.
- Mifepristone + Misoprostol once

B. Parenteral Progestin Preparations

- Slow release progestins: Medroxyprogesterone acetate (Depo-Provera®) given i.m. every 3 months. used in lactating females. Can lead to amenorrhea and osteoporosis. (Contain high levels of progestin)

- SC implant progestin (norgestrel) →. 5 years. (6 capsules are placed SC in upper arm).

Sex hormones

❖ Mechanism of Action

- Inhibit ovulation by –ve feed back → inhibition of FSH & LH
- Produce endometrial changes and interferes with coordinated contraction of the cervix, uterus, and fallopian tubes → inhibit implantation. (by both estrogen and progestins).
- Increase viscosity of cervical mucus to inhibit sperm penetration. (by progestins mainly)

❖ Therapeutic uses:

1. Contraception
2. Dysmenorrhea , endometriosis (Large dose of Progestins). .

❖ Adverse effects

- Most of the adverse effects are due to Estrogen
- The risk of side effects increases in women above 35 and heavy smokers

1. ↑ Risk of thromboembolism, myocardial infarction , Hypertension and cervical cancer and breast cancer.
2. Weight gain and edema , headache and nausea, gall stones. Cholestatic hepatitis and hepatotoxicity.
3. Amenorrhea
4. Progestins causes depression, hirsutism and acne.

Sex hormones

❖ Contraindications:

- Hypertension or ischemic heart disease (IHD).
- History of embolism, thrombosis or cerebral hemorrhage.
- cancer breast or estrogen-dependent neoplasm
- Chronic liver disease and gall stones.
- Diabetes mellitus.
- smokers, or women over 35 years. - Pregnancy.
- Depression
- Undiagnosed vaginal bleeding (which may be due to endometrial carcinoma).

❖ Drug interactions:

- Drugs that HME inducer as rifampicin, Phenobarbital, Phenytoin, Carbamazepine, & Tobacco smoking → ↓ efficacy of oral contraceptives' → pregnancy.
- Paraffin oil (laxative) ↓ intestinal absorption of contraceptive pills.
- Oral contraceptives may decrease the efficacy of warfarin & sulfonylureas

Sex hormones

❑ Androgens (Androgenic/Anabolic Steroids) (AAS)

- The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females.
- Testosterone (the main androgen) is synthesized naturally by testis under the control of L.H.
- Testosterone+ F.S.H. → Seminiferous Tubules → Spermatogenesis → Fertility.

  - But Testosterone Alone in large dose → ↓ F.S.H. & ↓ L.H. → ↓ Spermatogenesis.

- **The androgens are required for:**

  - spermatogenesis, increases libido
  - ↑ synthesis of muscle proteins and hemoglobin.
  - Vitamin D activation &increase calcium deposition in bone
  - Increase growth hormone receptors
  - Inhibition of insulin action
- Synthetic androgens have long t½ with more specific action.

❖ Examples of androgens:

- **Natural androgens**: Testosterone ineffective orally
- **Synthetic androgens**: Testosterone propionate in oil → I.M. .
- **Anabolic steroids**: nandrolone, stanazol. – Oxandrolon, Fluoxymesterone (Oral semi-synthetic androgen)

Sex hormones

❖ Therapeutic uses:

- Aplastic anemia, Anemia associated with acute renal failure, Osteoporosis, General wasting and Increase body mass and muscle strength in body builders (anabolic effect)

- Treatment of primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary).

❖ Adverse effects

- Masculinization, acne in females.
- High doses can cause impotence, decreased spermatogenesis and gynecomastia in males.
- Increase incidence of cancer prostate
- Hyperlipidemia, edema and hepatic disturbances. (in high doses)
- **Contraindicated** in cancer prostate

Sex hormones

❑ Anti-Androgens:

- Acting by interfering with the synthesis of androgens or by blocking their receptors.
- Finasteride is used in benign prostatic hyperplasia. Treatment of hirsutism in females. (inhibit 5-α reductase → ↓ conversion of testosterone to dihydrotestosterone)
- Flutamide & Cyproterone are used orally in hypersexuality and prostatic cancer. (compete with testosterone receptors)
- Ketoconazole: Antifungal and also inhibits synthesis of androgens and cortisol.
- spironolactone is a competitive blocker of both aldosterone and testosterone receptors. It is used in hirsutism in females.

Antimicrobials drugs

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Introduction of antimicrobials

- The term **chemotherapy**: was chemical substances (drugs) used to kill or stop growth of infective microbes (Antimicrobials), now drugs to kill cancer cells (anti-cancer chemotherapy).

❖ Chemotherapy includes:

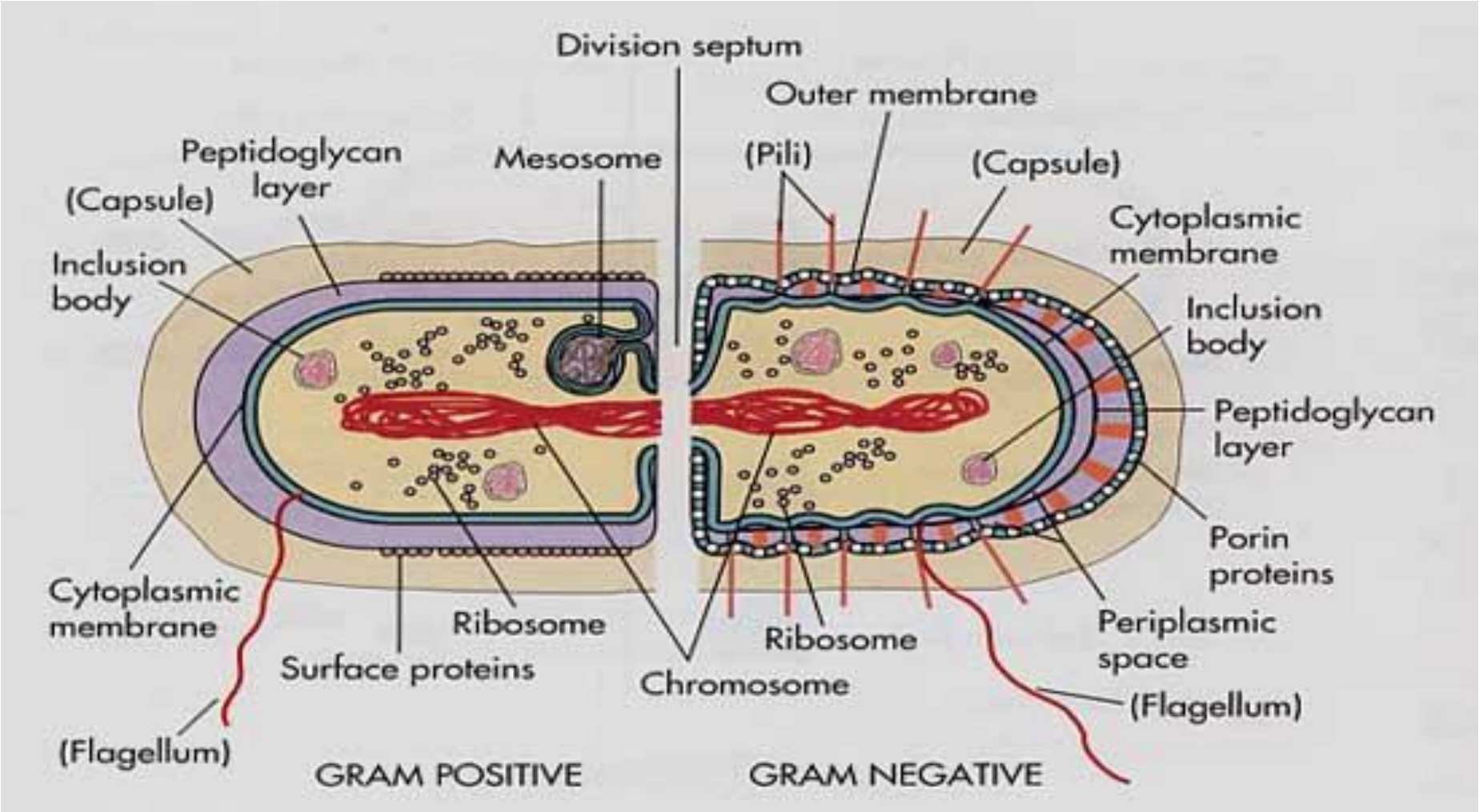
1. **Antimicrobial Agents**
   - They include **antibacterial, antifungal and antiviral drugs**.
   - **Antibiotics** are chemotherapeutic agents derived from living organisms (bacteria, fungi or mold) to be used to kill or stop growth other microorganisms as Penicillins , cephalosporins , tetracyclines, chloramphenicol

2. **Antiparasitic Agents**
   - Anthelmintics and antiprotozoal drugs.

3. **Anticancer Chemotherapy**

Classification of Bacteria

❖ **Bacterial structure**



Classification of Bacteria

❖ Classification of Bacteria:

1. According to Pathogenicity

A- Non-pathogenic: as normal flora (Staphylococcus epidermidis, Lactobacillus acidophilus

B- Pathogenic: as Neisseria gonorrhea, Streptococcus pneumoniae.

2. According to Growth Requirement :

A- Aerobics: most of bacteria.

B- Anaerobic: as, clostridium spp.

3. According to Gram Staining :

A- Gram positive (Gm +ve)

B- Gram negative (Gm-ve)

C- Non-Gram Stain bacteria (Atypical bacteria): as Mycoplasma, Chlamydia , Mycobacteria and Legionella.

NB:

- **MRSA**: Methicillin-resistant Staphylococcus aureus.
- **Pseudomonas aeruginosa.**

Classification of Bacteria

Types of pathogenic bacteria

Gram +ve bacteria

Gram +ve cocci	Disease	Gram+ve bacilli	Disease
Staphylococci *MSSA - MRSA *Vancomycin resistant	-Skin infections -Acute endocarditis Surgical wounds -Osteomylitis -Diabetic foot -Urinary tract infections	-Corynobacerium	-Diphteria
Streptococci	-Upper respiratory tract infections • tonsillitis, pharyngitis, otitis, sinusitis. - Lower respiratory tract infections: bronchitis & pneumonia -Sub acute endocarditis (Rheumatic fever).	Bacillus anthrax	Anthrax
Enterococci	-Peritonitis. -Urinary tract infections -Gastroenteritis - Endocarditis	Closterium botulonimi Clonstridium tetani	-food poisoning -Tetanus
		Listeria monocytogenes	-Meningitis in neonates

Classification of Bacteria

Gram –ve bacteria

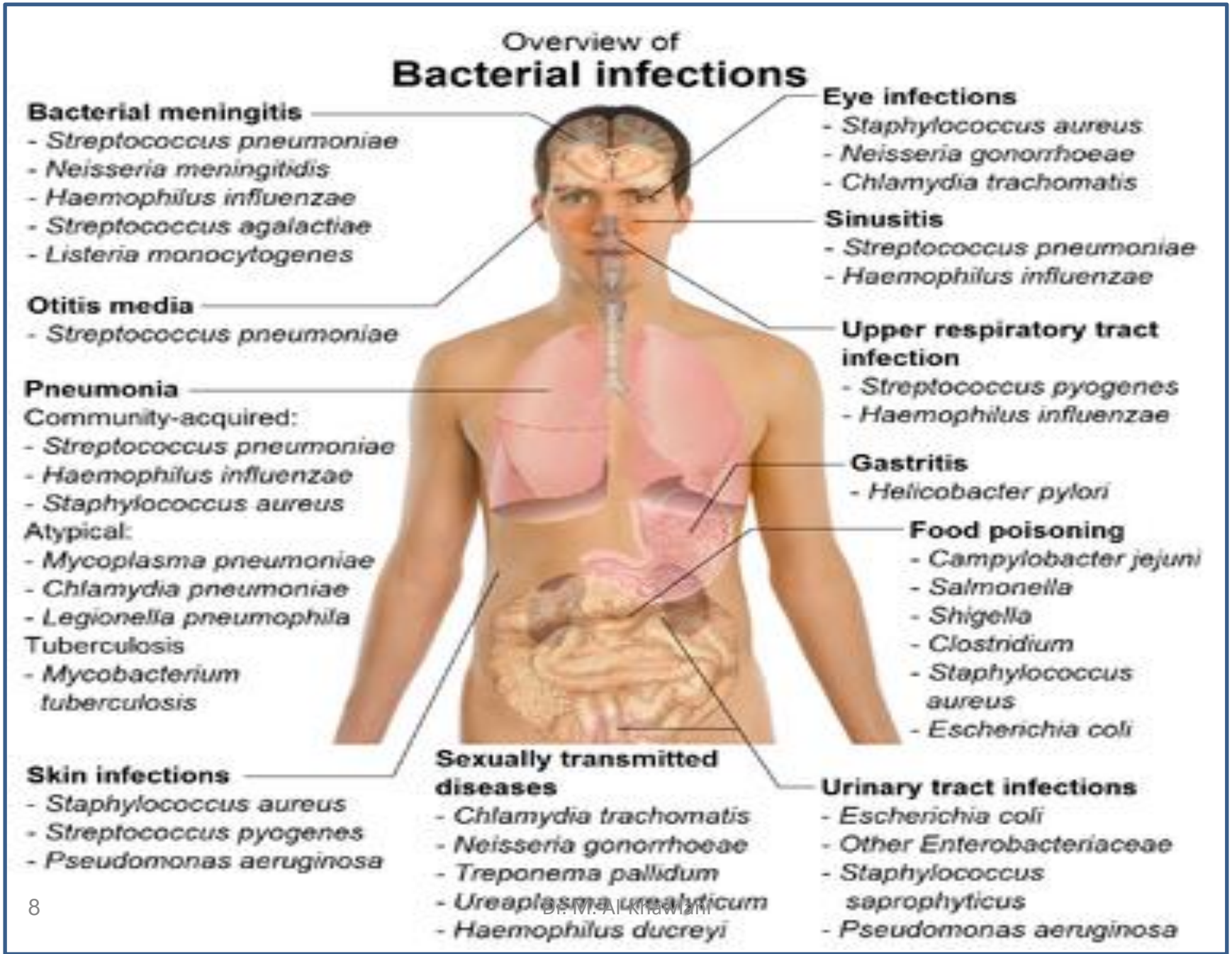
Gram-ve cocci	Disease	Gram-ve bacilli	Disease
-Neisseria meningitis	Meningitis	**In respiratory tract**	
			-Lower respiratory tract infect.
Niseeria gonorrhea	Gonorrhea	Hemophilus influenza	- Meningitis
		Potadella pertussus	-Upper respiratory tract infect.
-Moraxella	-Upper respiratory tract infections (URTI) • tonsillitis, pharyngitis, otitis, -Conjunctivitis	**-In urinary tract infections** (enterobacilli) -E. coli, kelpsiella , proteus, enterobactrer Serratia Pseudomonas	-Urinary tract infections -Gastroenteritis -Aspiration pneumonia -Neonatal meningitis
Pneumococci *Non penicillin producing *Penicillin producing	-Meningitis -Pneumoni	**In small intestine** Vibro cholera -Salmonella typi&paratypi -Brucella -yersenia	-Cholera -Typhoid fever -Brucellosis -Plague
		In large intestine -shegella & salmonella	Gastrointeritis
		In stomach& duodenum Helicobacter pylori Cambellobacter pylori	-Peptic ulcer -Deodenitis
		Psudomonas	-Urinary tract infections -Nosocomial infections -Infections in immuno-suppressed persons

Classification of Bacteria

Anaerobes	Disease	Atypical bacteria	Diseases
-Peptidococci -Peptidostreptococci	-Localized abscess in lung ,brain , root of teeth , pelvis , genital organs	**In genital tract** -Treponema -Chlamydia	 -Syphilis - Uro-genital infect. Pneumonia, Eye infections (trachoma).
-Clostridium perfingis	Gas gangrene	**In central nervous system** Rickettsia -Borrelia	 -Rocky mountain fever -Lyme diseases
-Clostridum difficle	Pseudomembranous colitis	**In respiratory tract** Nocardia Mycoplasma Myobactrium TB	 -Nocardiosis -Atypical pneumonia -Tuberculosis
-Propriobacterium acne	Acne valgais	Bones	Actinomycosis

G-ve = GIT, UTI, RTI, meningitis **G +ve**= RTI & skin

Classification of Bacteria



Antibacterial drugs

Antibacterial drugs

❖ Antibacterial drugs (antibiotic)

- Drugs or substances that used to inhibit the growth or kill bacteria.

❖ Classification of antibacterial drugs:

1. According to their source:

A. Natural: from fungi e.g. Penicillin

from bacteria e.g. Gentamycin

B. Semisynthetic: e.g. Ampicillin

C. Synthetic: e.g. fluoroquinolones.

2. According to the activity of the drug:

a) Bacteriostatic: stop growth and multiplication of bacteria, with the need for the body defense mechanisms (active immune) e.g. macrolides & tetracycline.

b) Bactericidal: kill the bacteria with no need for the body defense mechanisms (immune compromised patients active) e.g. B-lactam, vancomycin, co-trimoxazole and aminoglycosides. used in serious infections as endocarditis, septicemia, and meningitis.

N.B.:

- few antibacterial may be bacteriostatic or bactericidal according to their concentration or the state of activity of bacteria, e.g. erythromycin and isoniazid.

3. According to the spectrum of activity:

Broad spectrum	Narrow spectrum
-Effective against multiple gram +ve & Gm -ve organisms	-Effective against specific organisms
Imipenem , tetracycline, quinolones ,chloramphenicol , cotrimoxazole	**Antimicrobial against gram +ve bacteria** :macrolides , vancomycin ,Penicillin G **Antimicrobial against gram -ve bacteria**: aminoglycosides ,aztreonam
Used as initial empirical treatment till culture ,sensitivity results appear	-Used in treatment of susceptible organisms based on culture and sensitivity results
Rapid development of resistance	Slow development of resistance
-**Superinfection** with resistant strains and, pseudomembranous colitis are common	-Superinfection with resistant strains and pseudomembranous colitis are less common

3. According to their mechanism of action:

a) Inhibitors of cell wall synthesis: As: B- Lactam, vancomycin, cycloserine.

b) Inhibitors of protein synthesis by:

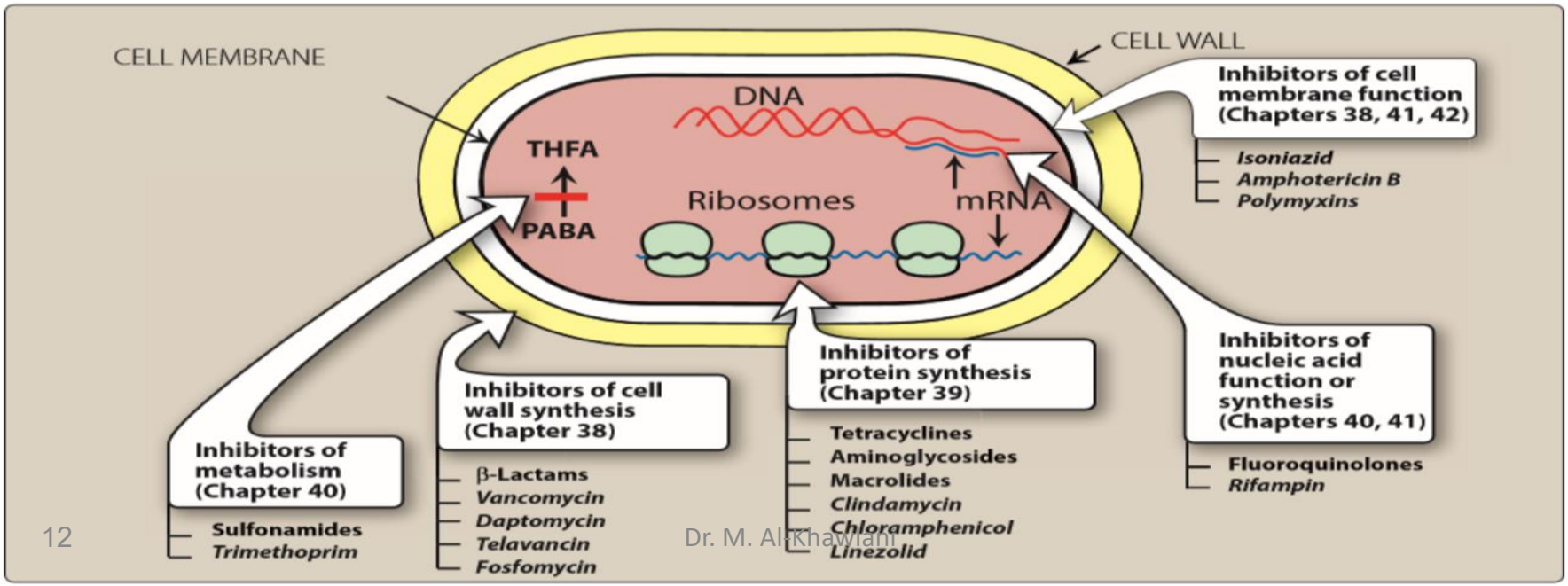
-Inhibition of 30 S ribosomal subunit As: tetracycline, aminoglycosides

-Inhibition of 50 S ribosomal subunit: As macrolides & Chloramphenicol.

c) **Inhibitors of nucleic acid synthesis**: As: rifampicin, quinolones.

d) **Inhibitors of cell membrane function**: As: daptomycin, isoniazid.

e) **Inhibitors of folic acid synthesis**: As: sulphonamides.



❖ Combination Therapy

❖ Advantages of drug combinations:

- **Provide broad spectrum** empirical therapying severely ill patient.
  As β-lactams + aminoglycosides
- **To achieve synergism**. as Amoxicillin + Clavulanic acid.
- **To treat mixed infections**. Diabetic foot
- **To ↓ development of resistant** strains e.g. in cases of TB infection.

❖ Disadvantages of drug combinations:

- Inhibition of bactericidal activity by bacteriostatic drugs → **Antagonism** (tetracycline → ↓ penicillin efficacy)
- Development of antibiotic resistance by giving unnecessary combination therapy.
- ↑ risk of superinfection.

1. Static + Static → Addition.
2. Cidal + Cidal → Synergism.
3. Static + Cidal → Antagonism

❖ Antibacterial resistance

- Antibacterial resistance is the ability of bacteria to grow in the presence of a drug that would normally kill them or limit their growth.

❑ Mechanism of resistance:

1- Synthesis of inactivating enzymes that destroy antimicrobial agents such as:
- Penicillinase produced by staphylococci, some streptococci , pneumococci , H. influenzas
- Gram –ve bacilli produces **Acetyltransferase** enzyme that inactivate aminoglycosides and chloramphenicol by transference of the acetyl group.

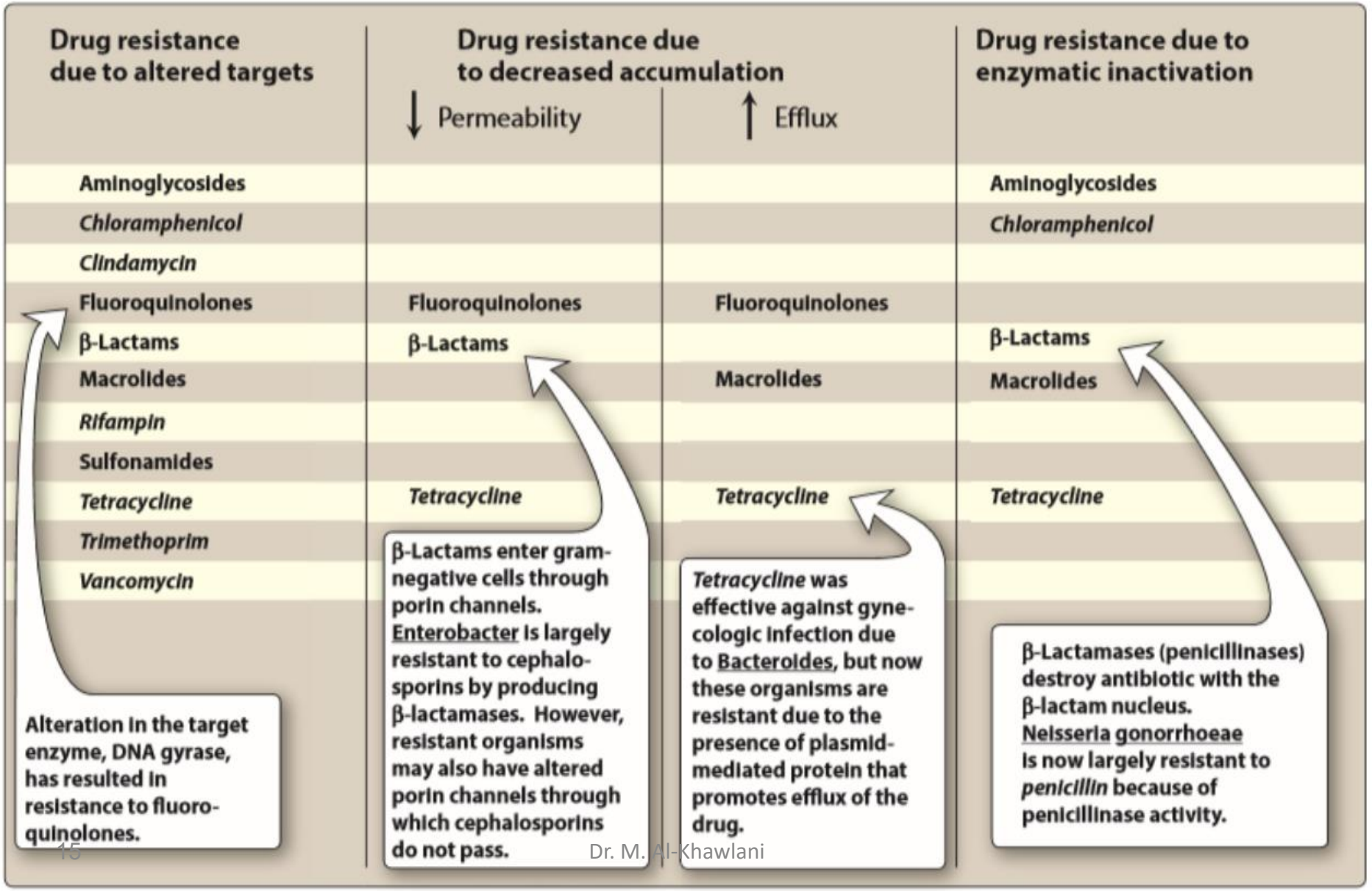
2- **Inhibition of entry of antibiotics inside the bacterial** cells eg pseudomonas and other g-ve bacilli inhibit the entry of aminoglycosides by loss or mutation of porins

- Increased efflux of an antibiotic by efflux pump that can transport drugs out of the cell. such as tetracycline

3- Target modification:

- Modification of the target site by chromosomal change.
  (As resistance against erythromycin and fluoroquinolones)
- Alteration of bacterial penicillin-binding proteins. (S. pneumoniae resistance to β-lactam)

Antibacterial drugs


Drug resistance due to altered targets
Drug resistance due to decreased accumulation
↓ Permeability
↑ Efflux
Drug resistance due to enzymatic inactivation
Aminoglycosides
Chloramphenicol
Clindamycin
Fluoroquinolones
β-Lactams
Macrolides
Rifampin
Sulfonamides
Tetracycline
Trimethoprim
Vancomycin
Fluoroquinolones
β-Lactams
Tetracycline
Fluoroquinolones
Macrolides
Tetracycline
Aminoglycosides
Chloramphenicol
β-Lactams
Macrolides
Tetracycline
Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoro-quinolones.
β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalo-sporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.
Tetracycline was effective against gyne-cologic infection due to Bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.
β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.

❖ Complication of antibacterial therapy:

1. Hypersensitivity (Anaphylactic reaction): Ex. **Penicillins**

- characterized by hypotension, bronchospasm, vascular collapse and may lead to shock..
- Treated mainly by adrenalin, hydrocortisone, antihistamines and oxygen.
- Test for allergy must be done. (Sensitivity test)

2. Direct toxicity

- High serum levels of certain antibiotics as; aminoglycosides may cause ototoxicity by interfering with membrane function in the auditory hair cells

3. Superinfections

- Broad-spectrum antimicrobials (as Clindamycin, fluoroquinolone) or combinations of agents → kill of the normal flora → overgrowth of opportunistic organisms, especially fungi or resistant bacteria as clostridium difficile → **pseudomembranous colitis** (antibiotic-associated diarrhea).

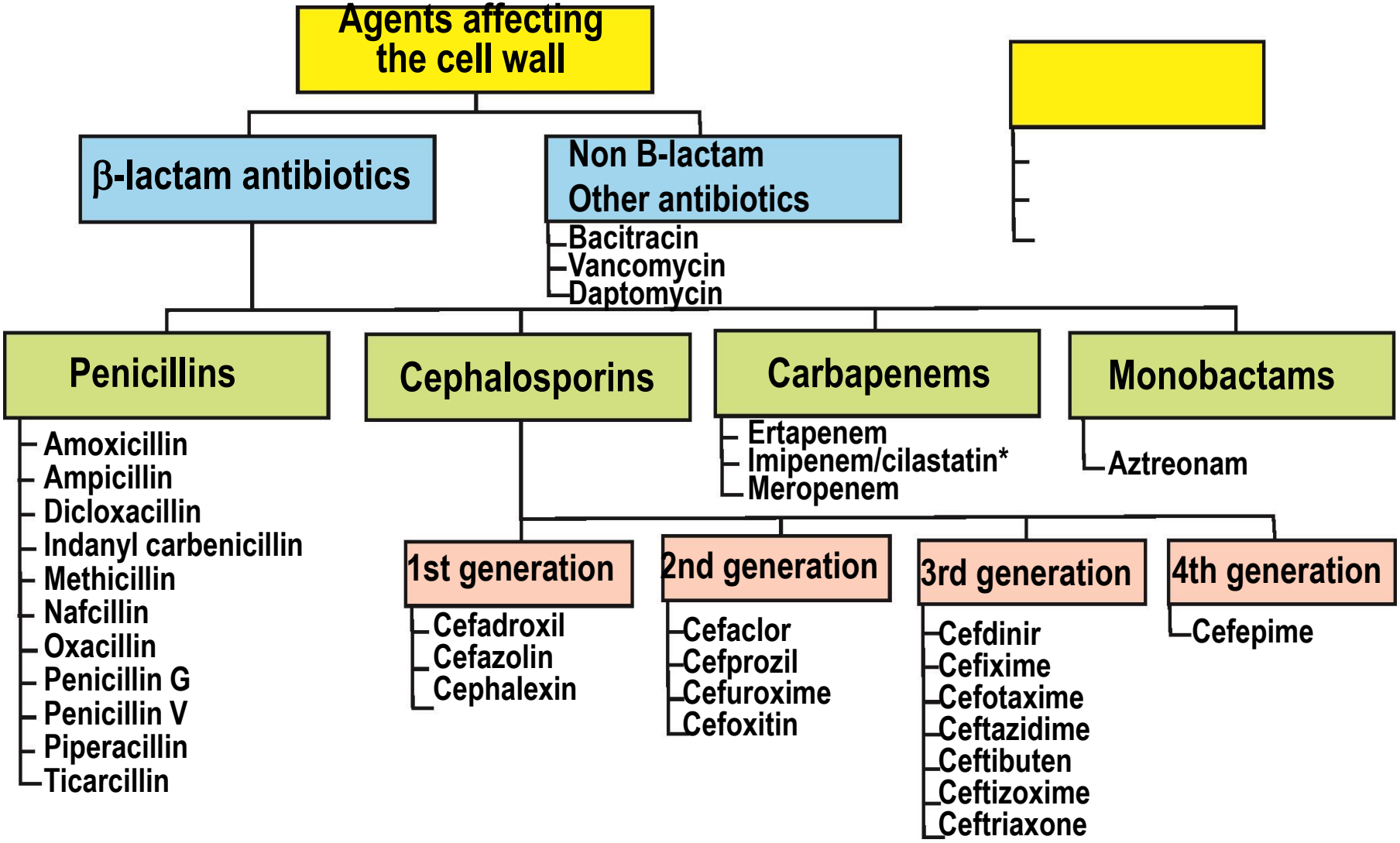
- **treatment by**: 1- Stop used the antibacterial drugs
  2- Metronidazole or Vancomycin orally
  3- Antifungal as; nystatin for candidiasis

Cell wall synthesis inhibitors

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❖ Inhibitors of cell wall synthesis:



(according to Lippincott´s Pharmacology, 2009)

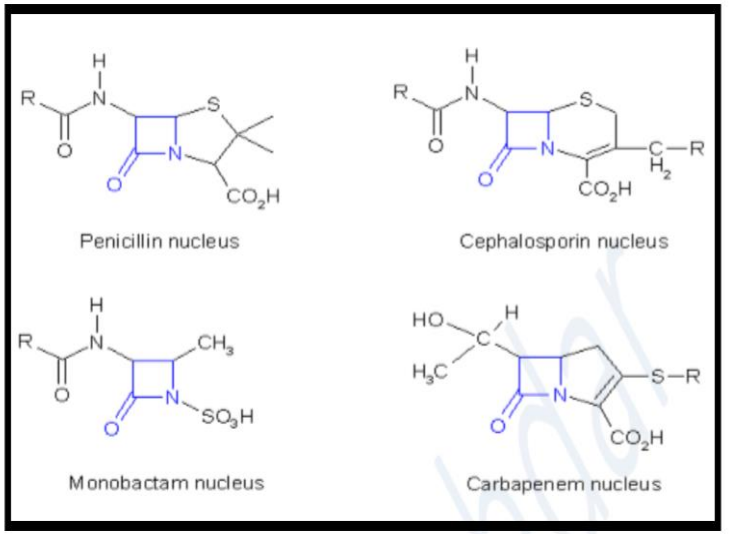
1 -B-Lactam Antibiotics:

AS: Penicillins, Cephalosporin, Carbapenem and Monobactam.

a) **Contain B-Lactam ring (**essential for anti-bacterial activity)

b) **Bactericidal and work in a time-dependent killing**

c) **They do not pass BBB** except in cases of inflammation, no hepatic metabolism

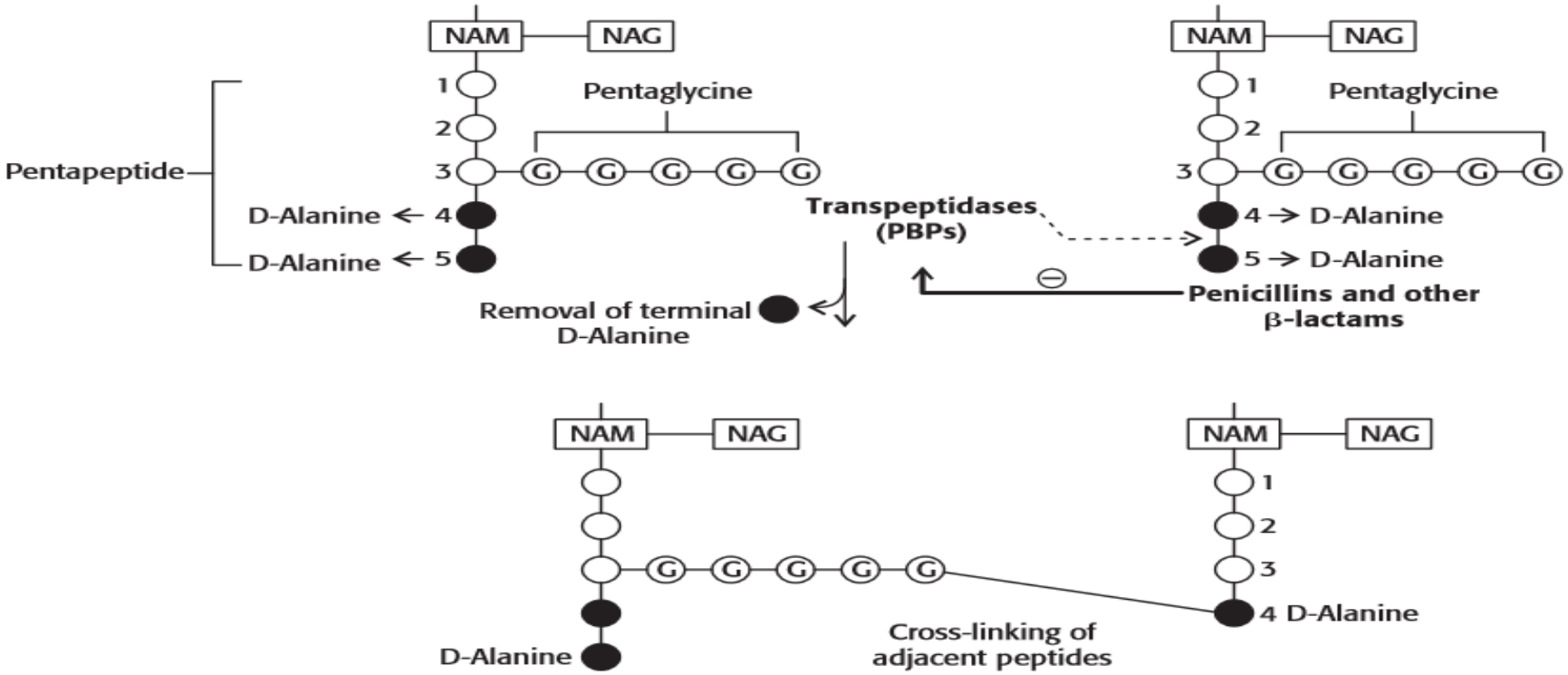


d) **M.O.A:** ↓ Cell Wall Synthesis by bind to specific Penicillin- Binding- Protein (PBP):

- ↓ Transpeptidase enzyme responsible for cross-linking of peptidoglycans, a final step in cell wall synthesis → ↓ Cell Wall Synthesis.
- Activate Autolytic enzymes (Autolysins) → Lysis of cell wall

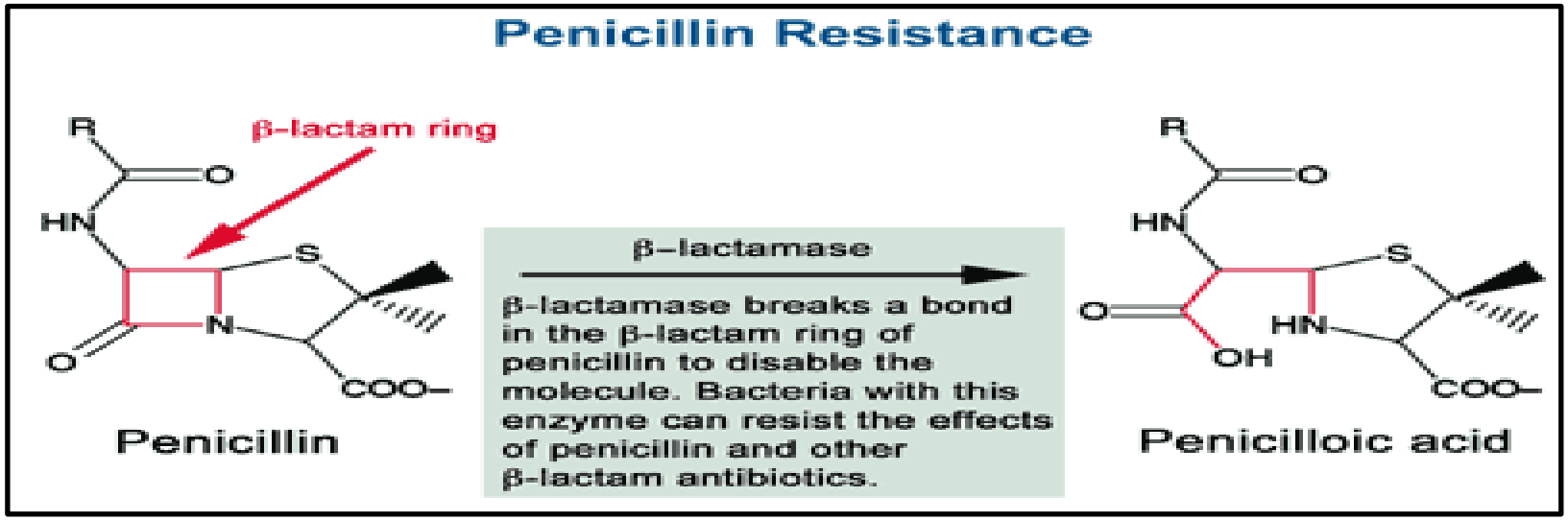
B-Lactam Antibiotics

- They affect mainly growing bacteria rather than resting one → have little or no effect on bacteria that are not growing and dividing
- No effect on organisms devoid of cell wall, e.g. Mycoplasma.
- **Selectivity:** Human cells do not contain peptidoglycan cell wall.



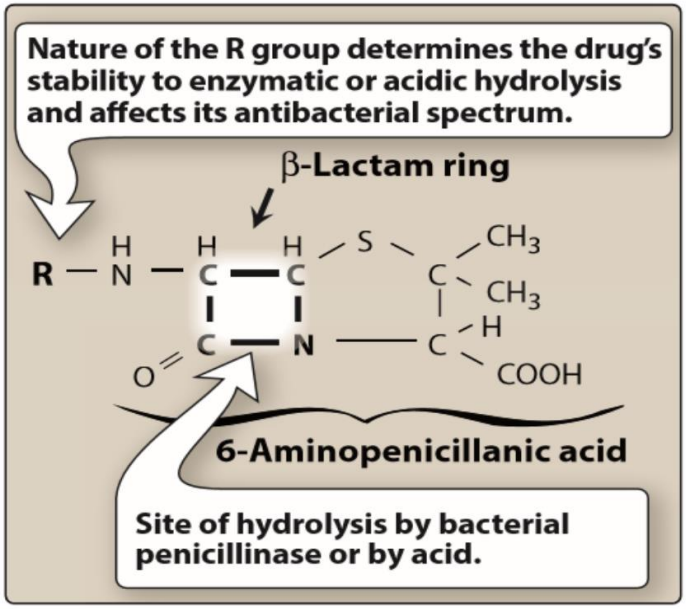
f) Resistance:

- **Natural absence of peptidoglycan cell wall** e.g. Mycoplasma, Mycobacteria, Fungi, and Viruses.
- **Production of B-lactamase enzymes**. penicillinases & cephalosporinases e.g. S. aureus, E.coli, H. influenza and Pseudomonas aeruginosa
- **Alteration in the PBP**; e.g. MRSA, Pneumococci and enterococci.
- **Decreased permeability to antibiotics** (eg, Pseudomonas due to loss porin)


Penicillin Resistance
β-lactam ring
Penicillin
β–lactamase
β-lactamase breaks a bond in the β-lactam ring of penicillin to disable the molecule. Bacteria with this enzyme can resist the effects of penicillin and other β-lactam antibiotics.
Penicilloic acid

1. Penicillins:

- They possess a common nucleus: 6-Aminopenicillanic acid with a B-lactam ring.
- Most widely effective and safer.
- Narrow spectrum (except ampicillin , amoxicillin)


Nature of the R group determines the drug's stability to enzymatic or acidic hydrolysis and affects its antibacterial spectrum.
β-Lactam ring
6-Aminopenicillanic acid
Site of hydrolysis by bacterial penicillinase or by acid.

- **Source**: :

  - **Naturally** from penicillium notatum **: penicillin G** & **penicillin V**

  - **Semi-synthetically: amoxicillin & ampicillin**

❖ Preparations of Penicillin

- The members of penicillin differ in:
  - Spectrum.
  - Stability to gastric acidity.
  - Susceptibility to bacterial B-lactamase.

1- **Natural penicillins**.as: **penicillin G** and **penicillin V**
2- **Anti- staphylococcal penicillin** as: **Methicillin**
3- **Extended—spectrum penicillin**: **Amoxicillin and Ampicillin (Aminopenicillins)**
4- **Antipseudomonal penicillin**. **Piperacillin & Carbenicillin**

Penicillin

A. Natural Penicillin: from penicillium molds

1. Benzyl Penicillin (Penicillin G):

- Rapid onset, The strongest effect.

1) **Acid-sensitive:** Not effect orally (given by IV injection).
2) **Inactivated by B-Lactamase (penicillinase)**: as Staph. aureus.
3) **Short acting** due to rapid excretion in urine (4-6 h).
4) **Narrow spectrum:** Gm+ve cocci & bacilli & Gm –ve cocci (not effect on all Gm-ve bacilli.

- **Gm + ve cocci**: against on all streptococci > non-penicillinase producing staphylococci > enterococci.
- **Gm + ve bacilli:** against all gm+ve bacilli :e.g. Cl. Perfringens (Gas gangrene)
- **Gm- ve cocci**: Gonococci and meningococci
- Some organisms: Treponema pallidum (syphilis) & actinomycosis (painful abscesses in the mouth, lung).

Uses:

- Treatment of **Serious infections:** meningitis (especially in babies, plus aminoglycoside), gas gangrene, syphilis
- Treatment of Diphtheria, anthraxs and subacute bacterial endocarditis and Acute rheumatic fever

❑ **NB:** gonorrhea.(Alternative: Ceftriaxone or fluorinated quinolones).

2. Phenoxy methyl Penicillin (Penicillin V): Weakest effect

1) **Acid-Resistant Penicillin:** effect orally
2) **Inactivated by B-Lactamase (penicillinase)**: as Staph. aureus.
3) **Short acting** due to rapid excretion in urine (6 h).
4) **Narrow spectrum:** against streptococcal

❑ **Used only in:** **Dose:** 250-500 mg /6-8 hours Orally.
- Treatment of minor infections as; streptococcal pharyngitis, (Amoxicillin is used instead).
- Prophylaxis in rheumatic fever (Streptococcal infections) 250 mg PO bid . (2nd choice).

.3. **Long acting penicillin** ,e.g. benzathine penicillin- procaine penicillin

- Insoluble salts of Penicillin G → allow slow drug absorption with long Duration of action

a) Acid-sensitive.
b) B-Lactamase-sensitive.
c) Narrow spectrum .
d) Long acting penicillin

-Procaine penicillin: given every 12 hours.
-Benzathine penicillin: given once/month.

Penicillin

1) Procaine Penicillin.

- Combination of penicillin G + procaine that have longer duration (12-24 h) and less painful
- **Used in:**

  - **As Prophylaxis** against subacute endocarditis in patients with valve disease or prosthetic valves before dental procedures, 2-3 hours before dental procedures. Or Amoxicillin 2 g (1 hour before tooth extraction).
  - **Treatment of** moderate cases: syphilis , gonorrhea.

- **Dose:** 600'000 U I.M /12-24 h**.**

2) Benzathine Penicillin (Retarpin)® :

- Slowest onset but has longest duration of action among penicillin

- **Used mainly in:**

- **As Prophylaxis in** rheumatic fever (β-hemolytic streptococcal infection), 1,200.000 units IM/ month for 5 years or until reaching 21 years age Or penicillin V 250 mg twice daily orally.
- **Treatment** of syphilis.
- **Dose:** 1.2 -2.4 million U I.M/ 1-4 Weeks.

B. Anti-staphylococci penicillin (B-Lactamase Resistant Penicillin)

Ex.

- **Methicillin** (given I.V only): It is not used now due to its nephrotoxicity
- **cloxacillin, dicloxacillin, nafcillin and flucloxacillin** (oral or parenteral)

a) Narrow spectrum
b) B-Lactamase (penicillinase) –resistant,
c) Acid resistant (except methicillin).
d) Semisynthetic penicillin.

- They are active against staphylococci and streptococci (weaker than penicillin G). but inactive against enterococci, anaerobic bacteria, and gram-negative cocci and rods.
- **Used** in the treatment of penicillinase producing staphylococci infections: as Abscess, skin and soft tissues infection
- Nafcillin (I.V, I.M) and Oxacillin (orally) are considered the drugs of choice for serious systemic staphylococcal infections
- **MRSA** (Methicillin-Resistant Staphylococcus Aureus) is a strain of Staphylococcus aureus that are resistant to β-lactam antibiotics. (drug of choice is vancomycin)

Penicillins

C. Extended-spectrum penicillin (Aminopenicillin): Semisynthetic penicillin

Ex: Ampicillin & Amoxicillin

a) **Acid resistant** (effective orally and parenterally).

b) **wider spectrum** (as natural penicillin + some Gram-ve bacilli).
- Gm -ve Bacilli e.g. H. influenza (R.T.I), E.coli (UT), salmonella typhi & H. pylori (GIT)
- **Not** effect on Pseudomonas, Proteus, and Klebsiella.

c) **B-Lactamase sensitive:** May combined with β– lactamase inhibitors **(clavulanic acid** or **sulbactam)** to enhance activity.
Ex: [Amoxicillin/clavulanic acid (Augmentin)® - Ampicillin/sulbactam (Unasyn®)].

1) **Ampicillin:** 250-500 mg/6 h, more active on shigella and H. influenza

- Incompletely absorbed orally especially in the presence of food, causing diarrhea and superinfection.
- **Useful** in enteritis (bacillary dysentery)
- Ampicillin + gentamicin is used for Listeria monocytogenes (bacterial meningitis) (**DOC**)

Penicillins

2) **Amoxicillin** (250-500 mg/TID): more active against Salmonella and Streptococcal fecalis.

- Absorption is much better than ampicillin (less affected by food than ampicillin) & longer duration and Less GIT disturbances & diarrhea

❖ **Use**:

- **RTI**: pharyngitis, tonsillitis, otitis, sinusitis, bronchitis, and pneumonia
- **Typhoid fever** and eradication of H. pylori in peptic ulcer.
- Prophylactically by dentists in **subacute endocarditis** before dental procedure (2 g/ 1 hour before tooth extraction).
- **U.T.I.**

❖ **B lactamase inhibitors:** : Clavulonic acid , Sulbactam , Tazobactam

- They bind with the enzyme → Irreversible inhibition → Suicide substrate.
- They have very weak or no anti-bacterial activity
- They protect penicillin from inactivation by B-lactamases secreted by some bacteria e.g. Proteus, E. coli, Pseudomonas, Staph aureus & H. influenza

❑ Clavulanic acid+ Amoxicillin (Augmentin)®. Oral, parenteral.
- **Uses**: - Acute otitis media, sinusitis, bronchitis, UTI.

❑ Sulbactam + Ampicillin Unasyn®. Oral, IM & IV.
Uses: Mixed intra-abdominal and pelvic infection.

Dr. M. Khaled

D. Anti-Pseudomonal Penicillin: Semisynthetic penicillin

Ex: Piperacillin (most potent) **& Ticarcillin, Carbenicillin**

a) **Inactivated by B-lactamase:** so they are combined with β– lactamase inhibitors (clavulanic acid or Tazobactam) to cover B-lactamase producing bacteria.
b) carbenicillin is acid stable (oral); piperacillin is unstable (parenteral).
c) **Broad spectrum**: including Pseudomonas & many Gram-ve bacilli.
- Less active against gm+ve bacilli and cocci.

- They are given with aminoglycosides (synergistic effect) → treatment of serious infections (pneumonias, UTI, burns) but should not be mixed in the same syringe or bottle.

- They are subdivided into:
  - Carboxy penicillins: **Carbenicillin** (IV, IM) **– Ticarcillin** (IV)
  - Ureido penicillins: **Piperacillin - Azlocillin- Mezlocillin** (IV, IM).

❑ Clavulanic acid + Ticarcillin (Timentin)®. IV, IM.
- Uses: Mixed nosocomial infection + aminoglycoside

❑ Tazobactam + Piperacillin (Zosyn)® IV.
Uses: Intra-abdominal, pelvic, urinary and respiratory infection.

❖ Pharmacokinetics:

A) Absorption: Most of penicillin are incompletely absorbed after oral administration → Superinfection - Most oral penicillin (Except amoxicillin) is impaired by food

B) **Distribution**:. low tissue distribution, not pass BBB except in cases of meningitis, Pass placental (safe in pregnancy).

C) **Excretion**: excreted unchanged (active) in urine, effective in treatment of UTIs (Except nafcillin & oxacillin, hepatic metabolism, biliary excreted).

- Probenecid inhibits renal tubular secretion of penicillin by competing with it For acid secretory mechanism. Thus, it prolongs penicillin action.

❖ **Side effects:** Penicillin are among the safest antibiotics

1) **Hypersensitivity** (allergic reactions):
   - As rash, urticaria, angioedema, or anaphylactic shock
   - There is cross allergy between penicillin and other B-lactam antibiotics

2) **Diarrhea, pseudomembranous colitis and superinfection** ; more with incompletely absorbed & broad spectrum agents eg. ampicillin.. → caused by C.difficile (treated by, Metronidazole or Vancomycin).

3) **Local pain** due to IM injection (penicillin G), thrombophlebitis after IV injection

4) **Neurotoxicity**: Seizures and epileptic fits in case of large doses and patient with renal failure.

5) **Decreased coagulation**: leading to bleeding (carbenicillin, ticarcillin), due to defective platelet aggregation

7) **Nephritis:** by methicillin (not used clinically).

❖ Drug interactions

- Penicillin + Tetracyclines, Chloramphenicol, Erythromycin → Antagonism.
- Penicillin + Aminoglycosides → Synergism (but should not be mixed in the same syringe → Inactive each other)
- Penicillin + Probenecid → Prolongs action of penicillin

❖ Contraindications:

- Allergy.
- Epilepsy

Cephalosporin

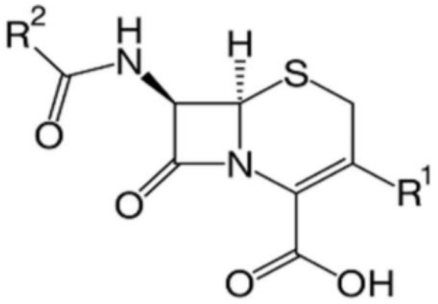
2. Cephalosporin:

- The cephalosporin are β-lactam antibiotics → related both structurally and functionally to the penicillin, but more resistant to certain β-lactamases → **Wider spectrum** of activity than penicillin.

- Derivatives of **7-Aminocephalosporanic acid**.

- The mechanism of action and resistance are similar to penicillin, → **Bactericidal** &↓ **cell wall synthesis**.

- All cephalosporin are **ineffective against**
  - MRSA (except 5th generation are active against MRSA & VRSA),
  - Listeria monocytogenes
  - Clostridium difficile
  - Enterococci . (except 5th generation , ceftaroline).
  - Atypical organisms



Chemical structure of Cephalosporins

Cephalosporin

❖ Antibacterial Spectrum:

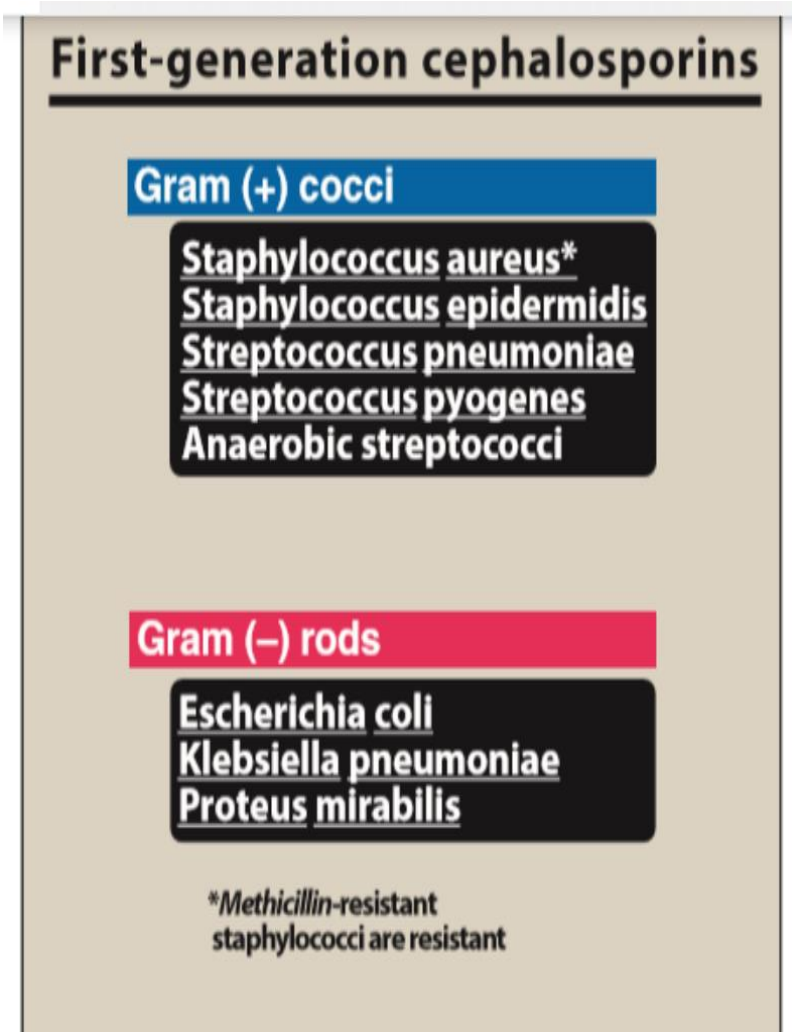
- Can be classified into five major groups or generations, depending mainly on the spectrum of antimicrobial activity and resistance to β-lactamases.

A) First Generation Cephalosporins: act as penicillin G substitutes.

❖ Preparation

- **Oral Preparations**: Cephradine, Cephalexin, cefadroxil
- **Parenteral IM & IV**: Cefazolin

- **Effect on Gm +ve** :Very highly Active against all except MRS and enterococci
- **Limited Gm –ve** (E. coli, proteus Spp and K. pneumoniae, making them effective for UTI).
- Moderate resistant to B-Lactamase enzymes.
- Do Not cross BBB. NOT effective in meningitis.



Cephalosporin

❖ Therapeutic uses:

- Cephalexin/cefadroxil/ cefazolin can be used for prophylaxis of bacterial endocarditis before dental procedures as alternatives to amoxicillin.

- **Skin and soft-tissue infections** due to streptococci and Staphylococcus aureus

- Cefazolin: 1st choice in surgical Prophylaxis & Orthopedic surgery:
  Parenteral, Penetrates bone well, Penicillinase resistant (Staph).

Dose: - Cephradine, Cephalexin, Cefazolin 25-50 mg/kg/d /6-8 h
- cefadroxil 25-50 mg/ kg/12 h







Dr. M. Al-Kirawlani

Cephalosporin

B) Second Generation Cephalosporins:

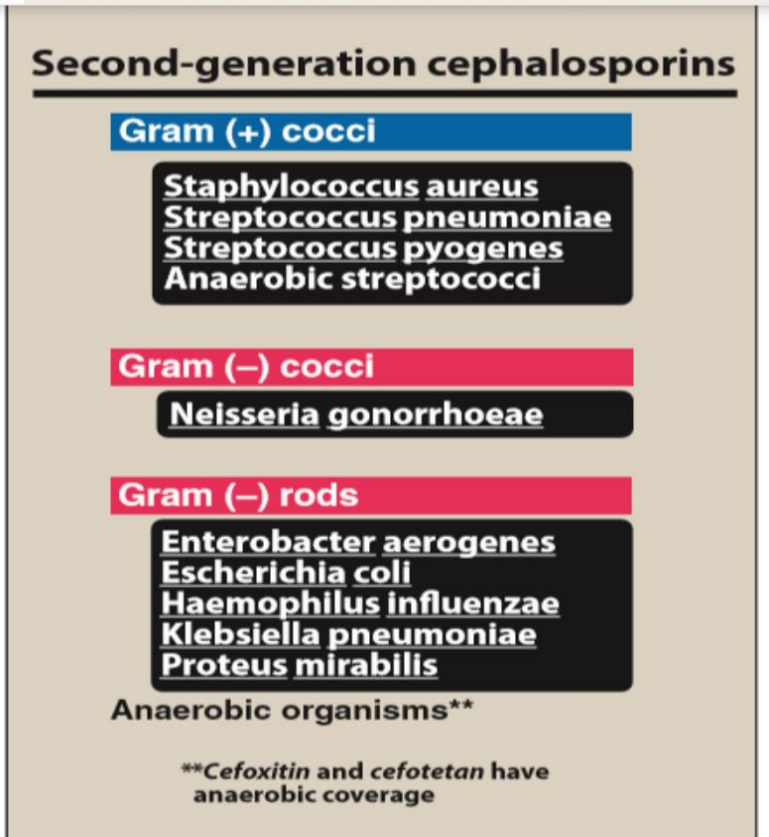
❖ Preparation

a) Oral Preparations: Cefaclore , Cefuroxime, Cefprozil

b) **Parenteral:**

- Cefotetan **&** Cefuroxime
- Cefoxitin: most active against anaerobes (Intra-abdominal, pelvic & gynecological infections),

- **Effect on Gm +ve** : Less active on G+ve than 1-generation. More active against streptococci, less active for staph.
- Extended spectrum on G-ve organisms e.g. (E. coli, proteus Spp, K. pneumoniae, H. influenza & Neisseria
- **Anaerobic bacteria (**Bacteroides fragilis**)**.
- More resistant to B-Lactamase enzymes.
- Do not cross BBB except cefuroxime (less effective in meningitis than ceftriaxone or cefotaxime



B) Second Generation Cephalosporins:

❖ Clinical Uses:

- Respiratory Tract Infection: sinusitis - otitis.
- Cefuroxime: also used in community acquired pneumonia (Long acting against H influenzae, K pneumoniae and also most pneumococci.)

- Cefoxitin and cefotetan are preferred for mixed (gram-negative bacteria and anaerobes) intra-abdominal and pelvic infections









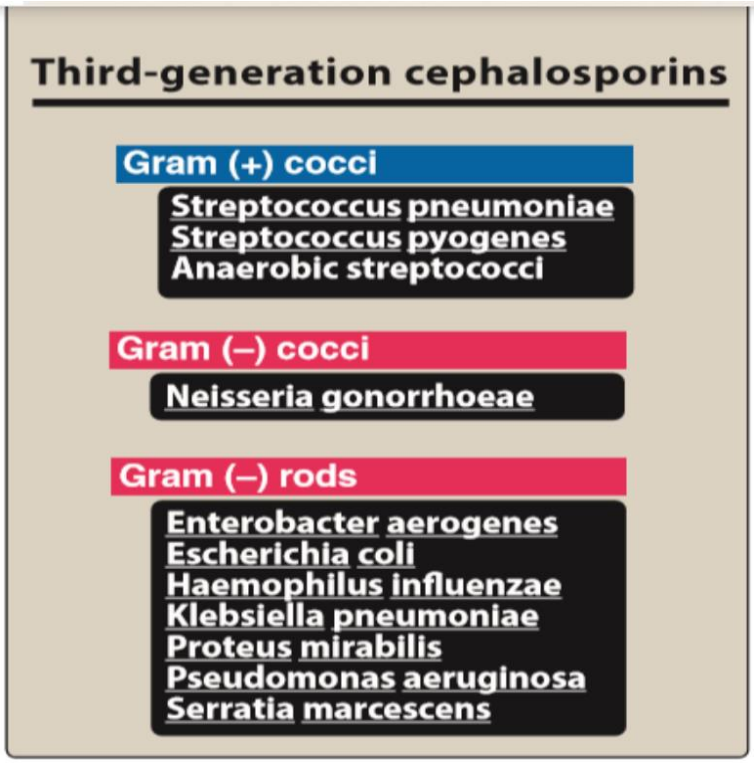
C) Third Generations Cephalosporin:

❖ Preparation

a) **Oral Preparations:** Cefixime & Cefpodoxime (100 mg bid).

b) **Parenteral** (IV & IM): Cefotaxime, Ceftriaxone, Cefoperazone, Ceftazidine, Ceftizoxime, Moxalactam

- **Less** effect on Gm +ve, **Very good activity** against Gm -ve.
- Ceftazidime & Cefoperazone are the only activity against **Pseudomonas aeruginosa**
- More Resistant to B-Lactamase enzymes.
- Penetrate to BBB in presence of meningitis **except** (cefoperazone and cefixime).
- They are excreted by the kidney, **except** cefoperazone & ceftriaxone excreted biliary allowing their use in renal failure.



C) Third Generations Cephalosporin:

❖ Clinical Uses

- Third-generation cephalosporins alone or with aminoglycosides are used in severe gram negative infections:

1. Meningitis caused by:
   - Pneumococci, meningococci, H influenzae: Cefotaxime & Ceftriaxone (preferred drugs)
   - Pseudomonas: ceftazidime + gentamycin .

2. UTIs, RTIs : Cefixime (200-400 mg OD)

3. Typhoid fever:(DOC) Ceftriaxone & Cefoperazone.

4. Gonorrhea: Ceftriaxone **(DOC)** & used in Septicemia

5. Community – acquired pneumonia**:** Pneumococci, H influenzae: Cefotaxime & Ceftriaxone

NB: They have long duration (12 hr) and ceftriaxone has longer duration (24 hr)

D) Fourth Generation Cephalosporin:

Preparation (parenteral IV) **:** Cefepime (i.v) & Cefpirome (i.m., i.v.)

- Combines the Gram-positive activity of first-generation agents with the wider Gram-negative spectrum of third-generation cephalosporins (Enterobacter species, E. coli, K. pneumoniae, Protuse, and P. Aeruginosa)

- More resistant to B-lactamase enzymes. passage across BBB.

Clinical uses: It is reserve drug for many serious infection like hospital- acquired resistant cases.

E) Fifth Generation Cephalosporin:

- Example: Ceftaroline: Given IV as a prodrug, ceftaroline fosamil

- Effective against Gram +ve (All including MRSA , vancomycin resistant , staphylococci + streptococci + enterococci)
- Gram –ve (as 3rd generation ceftriaxone).

- It is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia (activity against MRSA)

Cephalosporin

❖ Pharmacokinetics of cephalosporin:

- **Absorption** → Some are absorbed orally but most are given parentally.

- **Distribution** → All over the body as well as pass placental barrier and are safe in pregnancy
  - Several cephalosporin pass BBB as cefuroxime , 3rd (except Cefoperazone & cefixim) and 4th &5th generations to be useful for treatment of meningitis.

- **Fate:** excreted unchanged in urine mainly by tubular secretion and adding probenecid prolongs their action (must be adjusted in cases of renal dysfunction)

- Ceftriaxone and Cefoperazone are excreted in bile → used in patient with renal insufficiency.

❖ Adverse effects:

1. Allergy : (no anaphylactic shock) Only 1st generation has cross allergy with penicillin (10%).
2. GIT upsets and Superinfections
3. Nephrotoxicity; → especially if co-administration with gentamicin
4. Local reactions : IM preparations cause local pain at site of injection .IV preparation causes local thrombophlebitis

❖ Adverse effects:

5. **3rd generation may be cause**:
   - **Bleeding** due to inhibition of vitamin k activation, (cefoperazone, cefotetan) can be prevented by taken Vitamin K 10 mg twice weekly)
   - **Biliary obstruction** due to increase biliary excretion (cefoperazone & ceftriaxone).
   - **Disulfiram-like reactions** with ethanol and alcohol containing medications:

❖ Drug interactions:

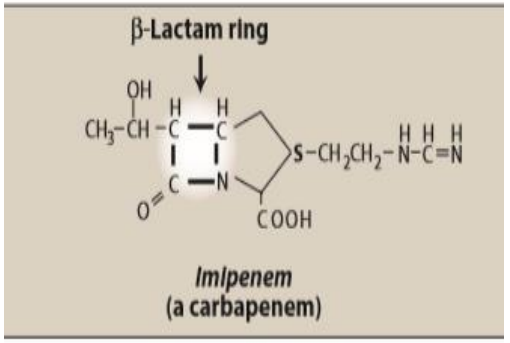
- If IV ceftriaxone + IV calcium-containing solution (e.g. Ringer's or parenteral nutrition)

- 3rd gene + ethanol or alcohol containing medications → augment of ethanol toxicity (inhibit ethanol metabolizing enzyme (aldehyde dehydrogenase) → nausea and vomiting (disulfiram-like reaction).

Carbapenems & Monobactam

3. Carbapenems:

- **Examples (given I.V)**: Imipenem , Meropenem, Ertapenem , doripenem
- Synthetic β-lactam antibiotics that differ in structure from the penicillin in that the sulfur atom has been replaced by a carbon atom.



- Imipenem, like other B-lactam antibiotics, acts by inhibiting bacterial cell wall synthesis and produces bactericidal activity.
- Very wide spectrum against all bacteria, aerobic and anaerobic Gm +ve and Gm- ve including P. aeruginosa except MRSA and vancomycin resistant staph.
- It is resistant to most B-lactamases.
- Given IV. Pass BBB during meningitis. Excreted unchanged in urine by tubular secretion.
- Imipenem is metabolized in renal tubular cells by dihydropeptidase into a nephrotoxic metabolite. The imipenem should be combined with a dihydropeptidase inhibitor as cilastatin.
- Imipenem + Cilastatin = Tienam® (catogray C)

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Carbapenems

- Doripenem, ertapenem and meropenem are similar to imipenem but have slightly greater activity against gram-negative aerobes and slightly less activity against gram positives.

- They are not significantly degraded by renal dehydropeptidase and do not require an inhibitor.

- All carbapenems except ertapenem have antipseudomonal effect .

❖ **Indications:** dose: 0.25-1g/6-8

- Multi-resistant bacteria Infections (resistant to other drugs) & in serious hospital acquired (Nosocomial) infections.

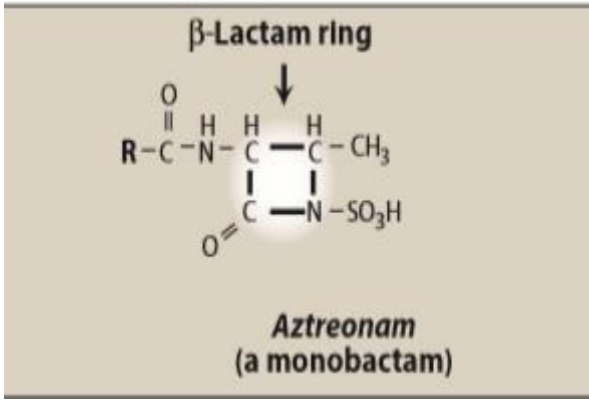
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- Mixed bacterial infections, such as urinary, respiratory, intra-abdominal, gynaecologic, skin, soft tissue, bone and joint infections.

❖ **Adverse effects:** More common with Imipenem:

- Nausea, vomiting, and diarrhea.
- Seizures (in large doses).
- Allergy and partial cross-allergy with penicillin and cephalosporin

4. Monobactam:



- **Example:** Aztreonam 1-2 g /6-8 hours IV, IM.
- It also acts by inhibiting the bacterial cell wall synthesis.
- It is effective only against gram-negative bacteria, such as, P. aeruginosa, gonococci and H. influenzae but has no activity against gram positive bacteria and anaerobes.
- It is resistant to most B-lactamases.
- It is administered only parenterally (i.m., i.v.).
- The main advantage with aztreonam is lack of cross-reactivity with other B-lactam antibiotics.

- **Uses:** .
  - In serious infection for Gm -ve infections in patient allergic to penicillin, cephalosporins, or carbapenems

❖ **Adverse effects:**

- Thrombophlebitis, skin rash.
- Increase hepatic serum transaminases

Non-B-Lactam Antibiotics

1. Non-B-Lactam Antibiotics (Glycopeptide AB):

Example: **Vancomycin** (500 mg/6 h or 1 g/12h vials Slow I.V. Infusion & oral 250 mg/6 h)

- It is Tricyclic glycopeptides.

- It has a narrow spectrum of activity on
  - Gram-positive cocci: S. aureus including MRSA, S. epidermidis, S. pyogenes, S. pneumoniae, S. viridans and Enterococcus.
  - Gram-positive bacilli: diphtheroids and Clostridium spp

❖ Pharmacokinetics:

- Poorly absorbed after oral administration, used Slow I.V. Infusion for systemic infections.
- Orally for antibiotic-associated C. difficile colitis (for local action)
- Excreted unchanged in urine by passive glomerular filtration (Readjust dose in Renal patients).

❖ Mechanism of action: **bactericidal**

- It inhibits synthesis of bacterial cell wall phospholipids and prevents polymerization of peptidoglycan → inhibit cell wall synthesis.

Non-B-Lactam Antibiotics

❖ **Resistance** to vancomycin in enterococci is due to the terminal d-Ala is replaced by d-lactate → decreased affinity of vancomycin for the binding site → building block

❖ **Indications:** **Vancomycin** (Category C)

1. Alterative to penicillin G in peniclin resistant and penicillin allergic patient in serious infections. Vancomycin is used in combination with aminoglycoside

2. **1st choice in Serious infections** caused by MRSA such as endocarditis, meningitis, bone pneumonia , osteomyelitis, etc.

3. **2nd choice in treatment of pseudomembranous colitis** (given orally).

❖ **Adverse effects**:

- Ototoxicity. Nephrotoxicity. phlebitis
- Red man syndrome: rapid IV infusion leads to histamine release causing V.D. of cutaneous blood vessels and flushing.
- Allergy: rash and fever.



2. Fosfomycin: category B

- It is bactericidal, inhibit of cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, which catalyzes the first step in peptidoglycan synthesis.
- It is active against many gm +ve and gm- ve organisms
- Fosfomycin is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate.

❖ **Indicated** in urinary tract infection as single dose 3g orally repeated after 2-3 days

❖ **Adverse effects** include diarrhea, vaginitis, nausea, and headache.

. 3. Cycloserine:

- Cycloserine is a structural analog of d-alanine and inhibits the incorporation of d-alanine into peptidoglycan pentapeptide, inhibition of cell wall synthesis.

- It is effect against mycobacterium TB and some gram-ve bacilli in urinary tract

- **Used:** Because of its potential neurotoxicity (tremors, seizures, psychosis), it is only used to treat tuberculosis as a 2nd line drug in T.B.

3. **Bacitracin:**

- Polypeptide bactericidal antibiotic.
- Interferes with a late stage in cell wall synthesis → inhibits cell wall synthesis.
- **It is active against** Gram positive bacteria.
- Bacitracin is poorly absorbed. Topical application results in local antibacterial activity without systemic toxicity.
- **Indications:** used topically only with neomycin or polymyxin as ointment in treatment of skin and wound infections; never used systemically because it is extremely nephrotoxic.

4. Daptomycin

- a bactericidal concentration-dependent killing effect, cyclic lipopeptide antibiotic.
- It is used in the treatment of infections caused by resistant gram-positive organisms, including MRSA and vancomycin resistant enterococci (VRE)
- Its spectrum of activity is similar to vancomycin but more rapidly bactericidal and active against VRE and S aureus, given IV only.
- It disrupt bacterial cell membrane which lead to leakage intracellular components

Indication: 4-6 mg/kg IV/ 24 h.

- Skin and soft tissue infections
- Treatment of bacteremia caused by S. aureus
- Treatment of endocarditis caused by S. aureus

NB: daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

- **Side effects:** myopathy → avoid with statins

6. Polymixin B:

- Basic polypeptide.disrupting the outer cell membrane → Leakage of macromolecules & electrolytes → Bactericidal action .
- Narrow spectrum (act on G- only).
- Polymyxin B is available in parenteral, ophthalmic, otic, and topical preparations.
- Used only locally (Due to their high toxicity) :
  a- Topically (Usually+ Neomycin) as eye drops or skin preparations.
  b- Orally (NOT absorbed) to sterilize the gut.

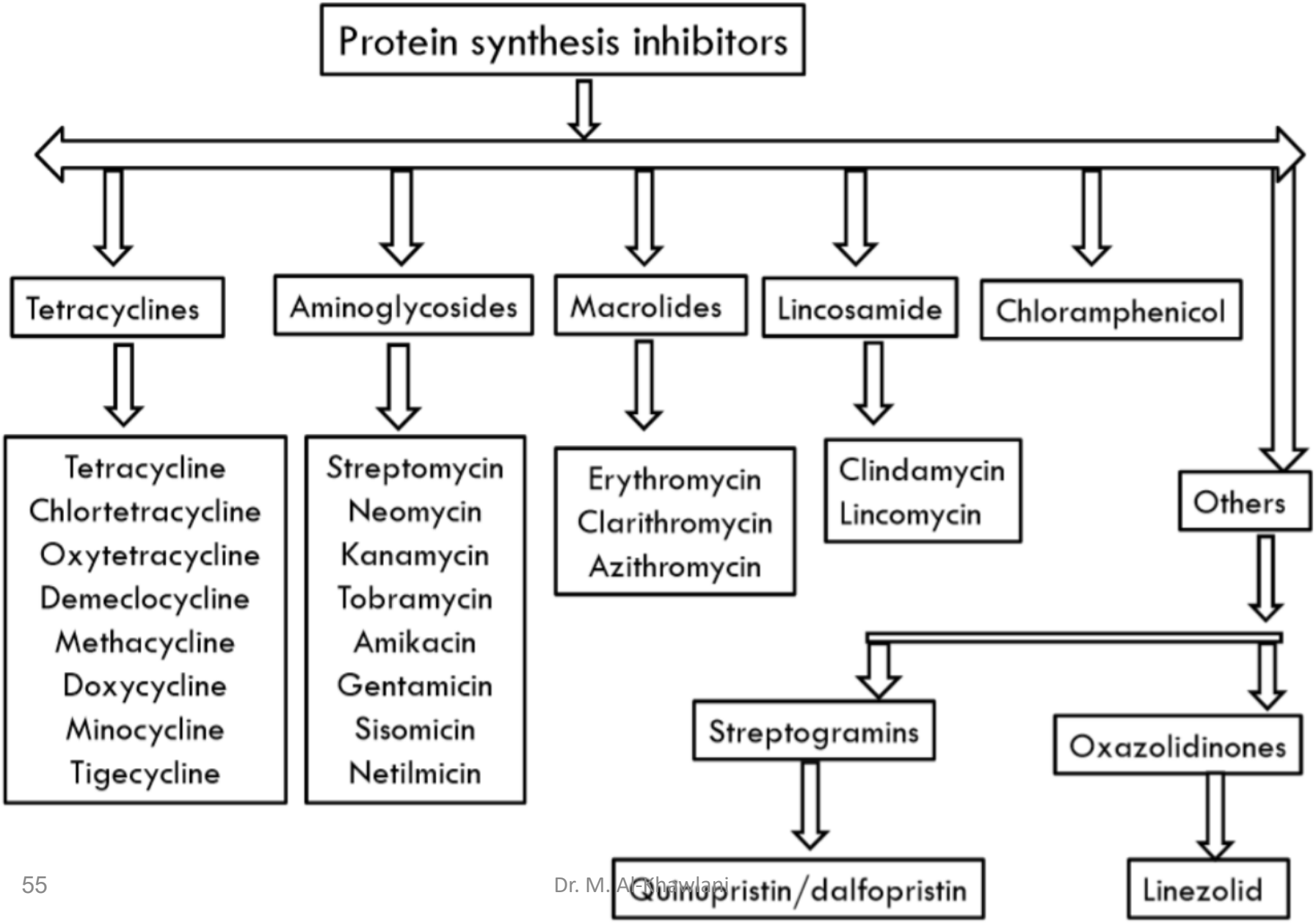
- Side effect: Nephrotoxic and neurotoxicity (slurred speech, muscle weakness)

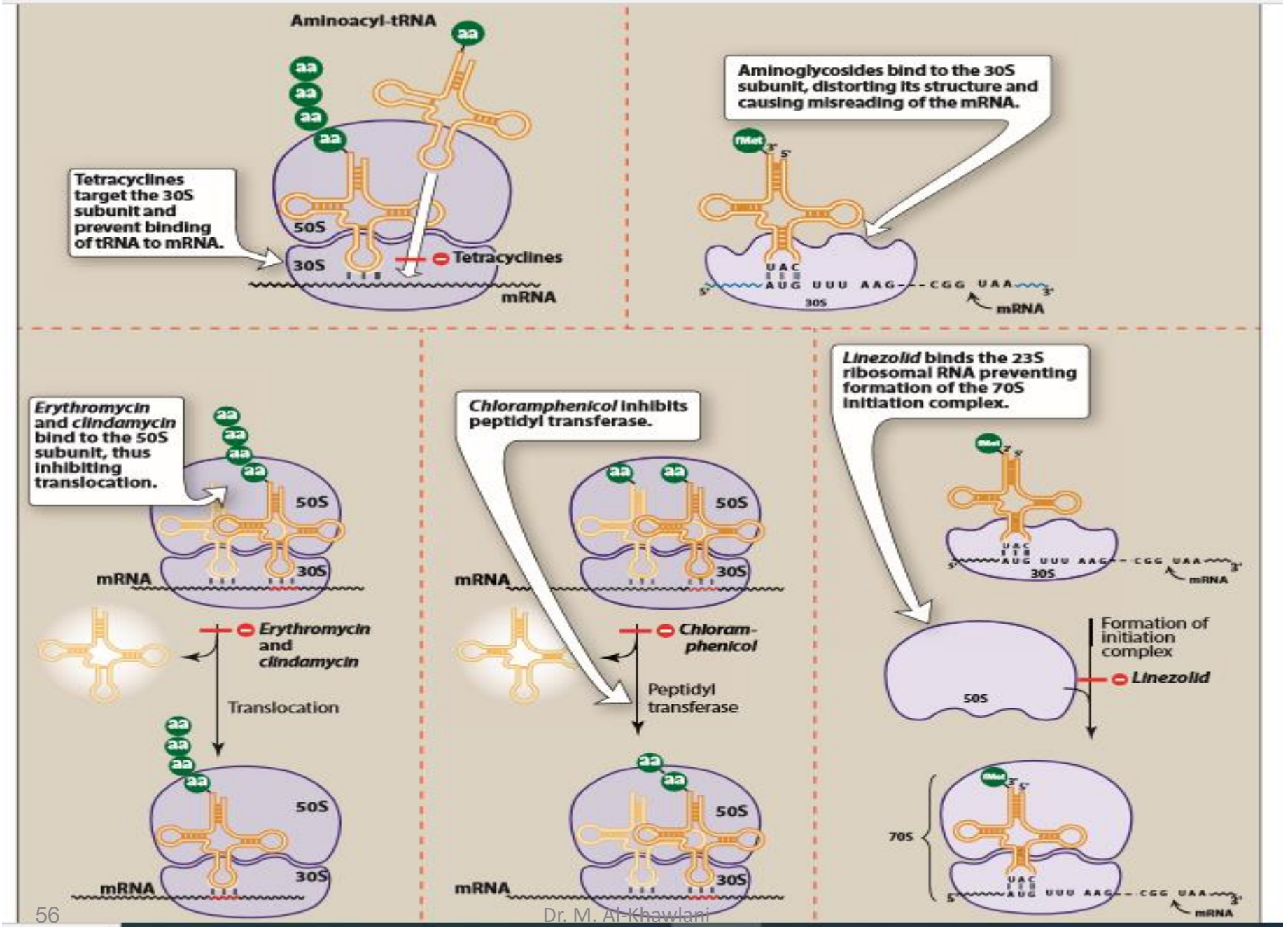
Protein synthesis inhibitors

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Assist. Professor of pharmacology and Toxicology

Protein synthesis inhibitors




Aminoacyl-tRNA
aa
Tetracyclines target the 30S subunit and prevent binding of tRNA to mRNA.
50S
30S
Tetracyclines
mRNA
Aminoglycosides bind to the 30S subunit, distorting its structure and causing misreading of the mRNA.
fMet
UAC
AUG UUU AAG CGG UAA
mRNA
Erythromycin and clindamycin bind to the 50S subunit, thus inhibiting translocation.
Erythromycin and clindamycin
Translocation
Chloramphenicol inhibits peptidyl transferase.
Chloram-phenicol
Peptidyl transferase
Linezolid binds the 23S ribosomal RNA preventing formation of the 70S initiation complex.
Formation of initiation complex
Linezolid
70S

PROTEIN SYNTHESIS INHIBITORS

Anti-Bacterial Class	Type of Inhibitor	Mechanism
Aminoglycosides	30S	Inhibits formation of initiation complex, causing the misreading of mRNA
Tetracyclines	30S	Prevents attachment of aminoacyl-tRNA to acceptor site
Chloramphenicol	50S	Inhibits *peptidyl transferase* (the enzyme responsible for incorporating new amino acid into growing peptide strand)
Macrolides	50S	Blocks aminoacyl-tRNA complex translocation step
Clindamycin	50S	Blocks initiation complex formation and inhibits aminoacyl-tRNA complex translocation step
Linezolid	50S	Blocks formation of initiation complex

Protein synthesis inhibitors

1. Aminoglycosides

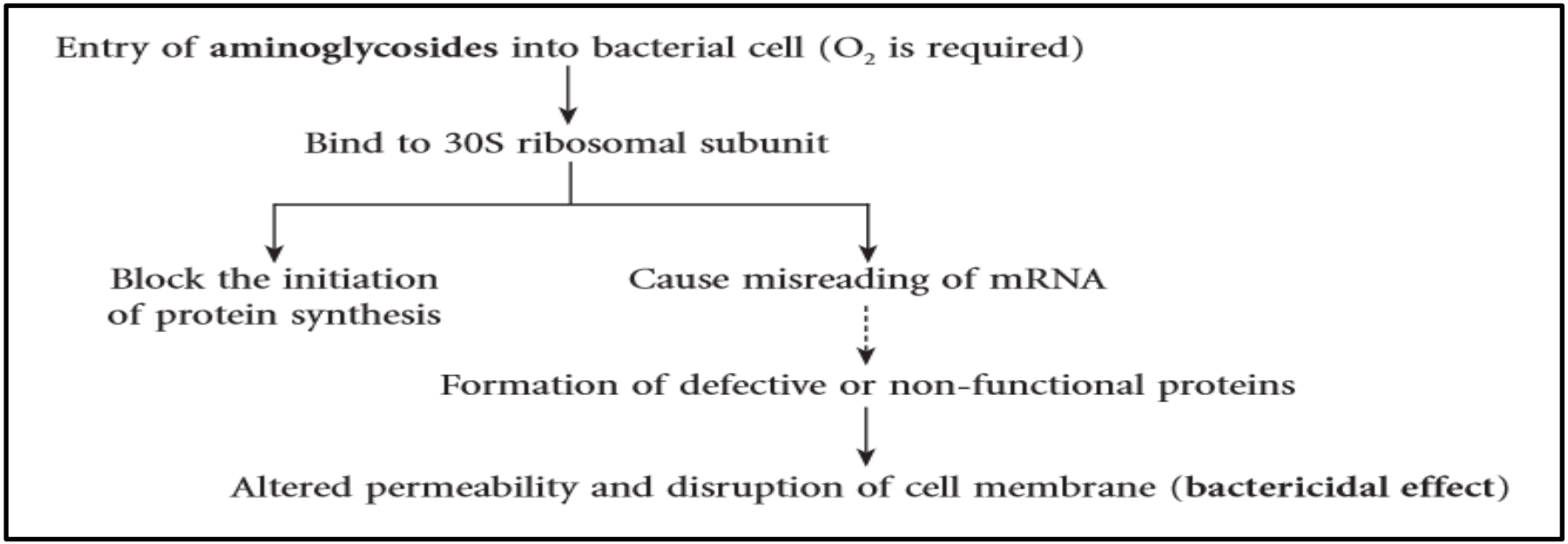
- Aminoglycosides are derived from either:
  - **Natural:** Streptomycin, Neomycin, Kanamycin, Tobramycin., Gentamicin, Netilmicin.
  - **Semisynthetic as:** Amikacin

❖ Common properties of aminoglycosides

1. Highly polar compounds (strongly basic) → poorly absorbed from the GI tract.
2. Given by parenteral route for systemic effect (**except** neomycin due to severe nephrotoxicity.
3. Cannot pass BBB even in meningitis.
4. Pass placental barrier → **fetal deafness**
5. Excreted unchanged in urine → **effective in UTI**. (dose adjustment is necessary in renal dysfunction. They become more active in alkaline urine.
6. Concentrated in renal cortex and in inner ear → **nephrotoxicity and ototoxicity**.
7. Effective against **gram-negative aerobes** organisms, e.g. E-coli, Pseudomonas, cholera.
8. Ineffective against **anaerobes** (requires 02 for transport into cells).
9. They exhibit a **concentration-dependent killing effec**t
10. They exhibit **post-antibiotic effect**

Protein synthesis inhibitors

- **M.O.A: bactericidal**, irreversible inhibitors of protein synthesis by binding to 30 S ribosomal


Entry of aminoglycosides into bacterial cell (O_2 is required)
Bind to 30S ribosomal subunit
Block the initiation of protein synthesis
Cause misreading of mRNA
Formation of defective or non-functional proteins
Altered permeability and disruption of cell membrane (bactericidal effect)

NB:

- Aminoglycoside entry can be enhanced by cell wall synthesis inhibitors, → antimicrobial **synergism** with B-Lactam antibiotics
- Never mix Aminoglycosides (Strong Base) with Penicillin (Acidic) in the same container or infusion fluid → Inactivation**.**

Protein synthesis inhibitors

❖ Resistance

- Bacterial that production of a **transferase enzymes** → inactivates the aminoglycoside
  - Amikacin resists to bacterial enzymatic inactivation, → the most effective Aminoglycoside against Gram-ve bacilli.

- ↓ Entry of drug into bacterial cell (**mutation or deletion of a porin** protein or proteins involved in transport)

- The receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation.

❖ Spectrum of activity: Narrow spectrum

- **High active against aerobic gram –ve bacilli**: Pseudomonas, Proteus & Klebsiella and Yersenia (plague).

- **In combination with a β-lactam antibiotic or vancomycin has effect on some Gm+ve cocci:** enterococci, streptococci and staphylococcal (MRSA) → used in the treatment of infective endocarditis (esp. Gentamycin).

- **Atypical organisms**: Active against mycobacterium TB. It is sensitive to Streptomycin

Aminoglycosides

❖ **Clinical Uses** (toxic, reserved for serious infections)

- **T.B.** (2nd line). Streptomycin + Rifampicin + lsoniazide + Pyrazinamide
- **Plague** (Yersinia pestis) & Tularaemia & Brucellosis: Gentamicin or Streptomycin + Doxycycline
- Pseudomonas infections (UTI) → Tobramycin (more effective) and Gentamicin.
- Bacterial endocarditis (prophylaxis before dental or other surgical procedures) → Gentamicin + penicillin G
- Enterococcus (patients allergic to B-lactam antibiotics) → Gentamicin + vancomycin .
- Topically (Cream, ointment or Solution) → burns, wounds, skin lesions and eye infections often in combination with polymixin B or bacitracin.→ Neomycin and Gentamicin.
- Bowel sterilization before surgery and endoscopy → orally **Neomycin**
- In Hepatic encephalopathy to suppress intestinal bacteria that produce ammonia → orally **Neomycin**

Aminoglycosides

- **Gentamicin:** most commonly used for aerobic gm-ve bacillary infections
- **Amikacin and** Netilmicin : It is resistant to aminoglycoside-inactivating enzymes, → effective against most of the gentamicin resistant and tobramycin-resistant bacteria.
- **Kanamycin**: Similar Neomycin. Used mainly orally & Topically
- **Paromomycin**: Direct Amebicide.1 g /6-8 hours orally.
- **Spectinomycin** (structurally related to aminoglycosides): In penicillin resistant Gonorrhea. 2 g I.M. ONCE

Aminoglycosides

❖ **Adverse effects:** narrow therapeutic index

- **Ototoxicity**: damage of 8 th cranial nerve (**deafness and vertigo**) esp. with other ototoxic drugs as loop diuretics (frusemide) & Chloroquine and in old age and with renal diseases

- **Nephrotoxicity**: esp. with other nephrotoxic drugs as cephalosporin, frusemide and NSAID.
  - The incidence of nephrotoxicity is highest with neomycin and least with streptomycin.

- **Skeletal muscle weakness (Neuromuscular paralysis):** ↓ Ach. Release

- **Allergic reactions:** Contact dermatitis is a common reaction to topically applied neomycin.

❖ **Contraindications:**

- Pregnancy.
- Renal impairment.
- Myasthenia gravis.

Aminoglycosides

❖ Precautions to reduce toxicity:

- Avoid using other nephrotoxic drugs as cephalosporin, amphotericin-B.
- Avoid loop diuretics because they are ototoxic and also increase the level of aminoglycosides in renal cortex.
- Reduce the dose or frequency of administration of aminoglycosides in patients with renal impairment. (40 mg./12 hours is less toxic than 20 mg./8 hours).
- Do not give high dose of aminoglycosides for more than 10 days.
- Never use aminoglycosides in pregnancy.

❖ Drug interactions:

- Amphotericin-B. Polymixins, Cephalosporins & Frusemide increase their Nephrotoxicity.
- Loop diuretics, & Chloroquine their Ototoxicity.
- With oral anticoagulants: oral aminoglycosides impair vitamin K production by intestinal bacteria potentiating the effect of anticoagulants.
- Aminoglycosides + Penicillins → Synergism. BUT NEVER mixed in same container.

2. Tetracyclines

- **Natural: from bacteria Streptomyces e.g. Chlortetracycline & Oxytetracycline**
- **Semisynthetic: Tetracycline & Demeclocycline**
- **Synthetics: Doxycycline & Minocycline.**

❖ Preparations & Pharmacokinetics

drug	Route of Administration	Absorption from the Gut (%)	Dosage	T1/2
A) Low to moderate Lipid Solubility (short acting):				
Tetracycline **Chlortetracycline** **Oxytetracycline**	Oral, I.V, topical	Incomplete	250-500mg/6h	6-8 h
Demeclocycline (intermetent acting)	oral	Incomplete	300-600 mg/12 h	12 h
B) High Lipid Solubility (Long-acting; given once/d):				
Doxycycline **Minocycline**	Oral, I.V	Complete	100 mg/12 h in day-1 then 100 mg /day 200 mg/12 h in day-1 then 100 mg /12h	16-18 h
Tigecycline (new agent- TC analog)	I.V		100mg I.V in day-1 then 50mg /12h	36 h

Tetracyclines

❖ Pharmacokinetics

- Incompletely absorbed orally, Affected by food
  - Absorption is decreased by food due to formation of non-absorbable chelates of tetracycline with Ca2+, Mg2, Al3+ (in antacids) and iron.
  - Doxycycline and minocycline→ Complete absorption, not affected by food (less chelates).

- **Distributed** all over the body. No cross of BBB (except doxycycline and minocycline

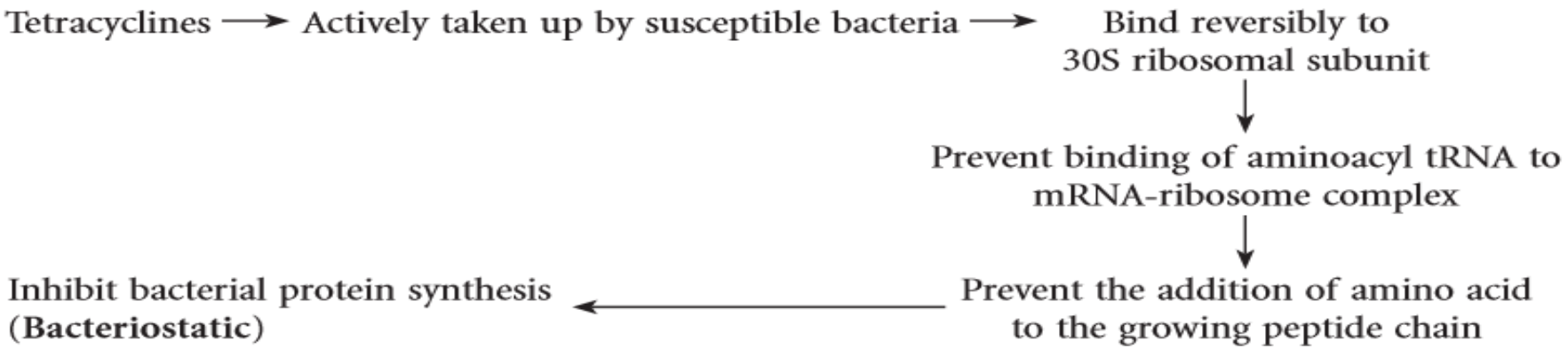
- **Pass placental barrier** and are teratogenic. Secreted in milk → affect the suckling infant.

- Concentrated at sites of calcification (Bone & Teeth) → damage growing bones and teeth. Tetracyclines are also concentrated in liver, skin and kidney.

- **Excreted**:
  - All tetracycline are excreted mainly unchanged in urine (useful in treatment of UTIs but the dose should be adjusted in renal impairment)
  - Minocycline: Urine, Milk, Tears & Saliva
  - Doxycycline: bile and can be used in renal impairment without dose adjustment

Tetracyclines

❖ **Mechanism of action**: Bacteriostatic


Tetracyclines
Actively taken up by susceptible bacteria
Bind reversibly to 30S ribosomal subunit
Prevent binding of aminoacyl tRNA to mRNA-ribosome complex
Prevent the addition of amino acid to the growing peptide chain
Inhibit bacterial protein synthesis (Bacteriostatic)

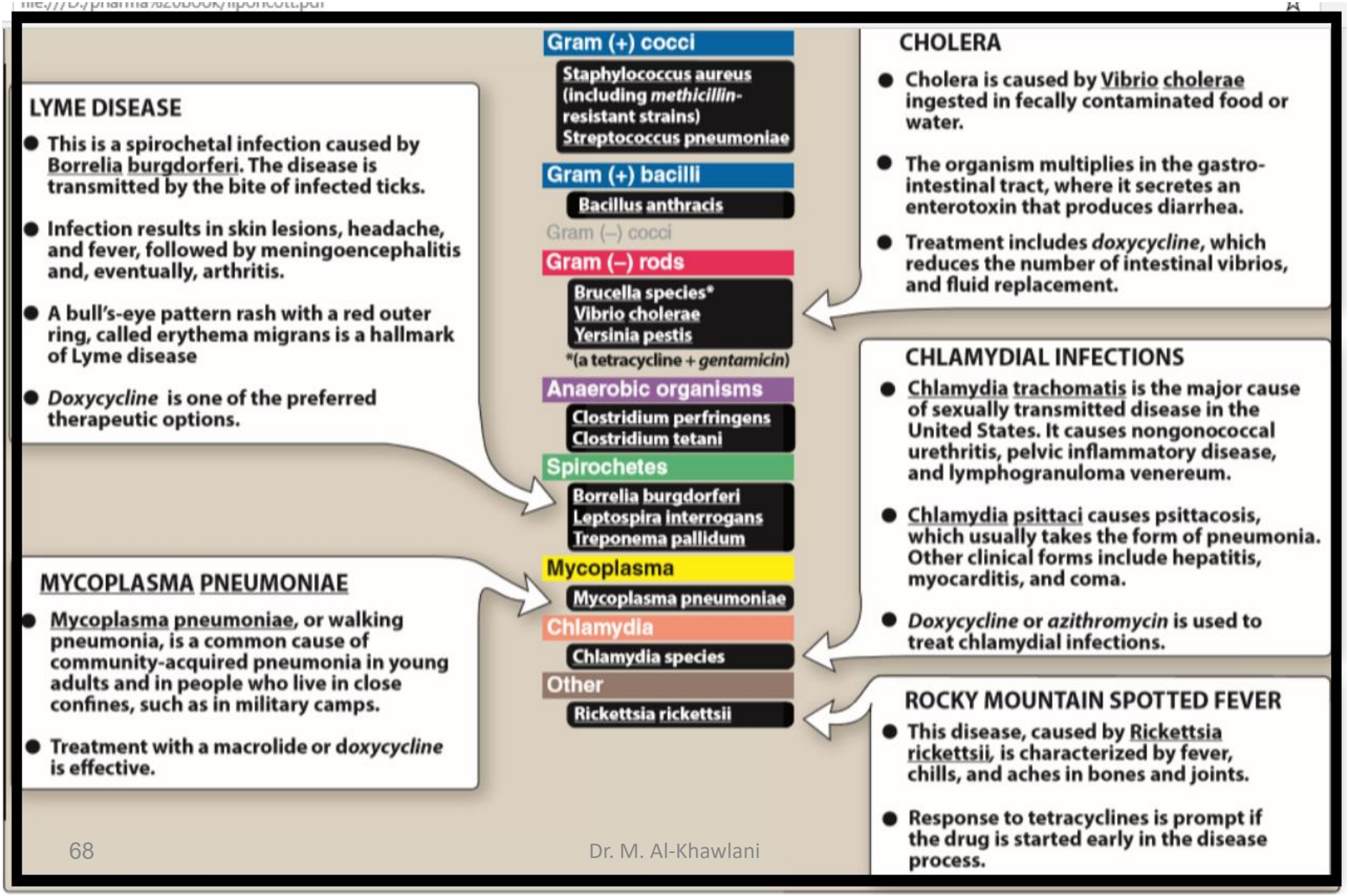
❖ **Resistance:**

1) ↓Accumulation (↓influx or ↑ efflux by an active transport protein pump)
2) Plasmid mediated synthesis of a 'protection‘ protein which protects the ribosomal binding site from tetracycline.

NB: Tigecycline is less susceptible than tetracyclines to bacterial resistance caused by ribosomal mutation and ribosomal protection proteins.

Tetracyclines

❖ **Spectrum of activity**: Tetracyclines have the broadest spectrum.


Gram (+) cocci
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus pneumoniae
Gram (+) bacilli
Bacillus anthracis
Gram (–) cocci
Gram (–) rods
Brucella species*
Vibrio cholerae
Yersinia pestis
*(a tetracycline + gentamicin)
Anaerobic organisms
Clostridium perfringens
Clostridium tetani
Spirochetes
Borrelia burgdorferi
Leptospira interrogans
Treponema pallidum
Mycoplasma
Mycoplasma pneumoniae
Chlamydia
Chlamydia species
Other
Rickettsia rickettsii
LYME DISEASE
This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
A bull's-eye pattern rash with a red outer ring, called erythema migrans is a hallmark of Lyme disease
Doxycycline is one of the preferred therapeutic options.
MYCOPLASMA PNEUMONIAE
Mycoplasma pneumoniae, or walking pneumonia, is a common cause of community-acquired pneumonia in young adults and in people who live in close confines, such as in military camps.
Treatment with a macrolide or doxycycline is effective.
CHOLERA
Cholera is caused by Vibrio cholerae ingested in fecally contaminated food or water.
The organism multiplies in the gastro-intestinal tract, where it secretes an enterotoxin that produces diarrhea.
Treatment includes doxycycline, which reduces the number of intestinal vibrios, and fluid replacement.
CHLAMYDIAL INFECTIONS
Chlamydia trachomatis is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
Doxycycline or azithromycin is used to treat chlamydial infections.
ROCKY MOUNTAIN SPOTTED FEVER
This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
Response to tetracyclines is prompt if the drug is started early in the disease process.

❖ Therapeutic uses

1. Drug of choice against:

- **Rickettsia infections** (rocky mount fever & typhus): (Doxycycline is given orally or i.v. for 5 –7 days):.

- **Chlamydial infections**: Doxycycline is the drug of choice. Macrolides are also effective.
  - uro-genital infection caused by C. trachomatis
  - Chlamydial Pneumonia caused by Chlamydia psittaci.

- **Mycoplasma pneumoniae infections:** Doxycycline or macrolides and Meningococcal carrier state (minocycline) but is now replaced by rifampicin

- **Cholera** (Single dose of doxycycline 300 mg orally, and fluid replacement

- **Brucellosis**: It is treated with a combination of doxycycline + rifampin or gentamicin or streptomycin

- **Lyme disease**: doxycycline .

2. 2nd choice against:

- syphilis, acne (Doxycycline 100 mg/12 h for 3 month), Anthrax and Plague.
- **Peptic ulcers** caused by Helicobacter pylori (tetracycline in combination regimens)
- **Malaria** and in the treatment of **amebiasi**s (doxycycline).

3. Demeclocycline decreases renal action of ADH and is used in patients with excessive ADH release known as Syndrome of Inappropriate ADH (SIADH).

❖ Tigecycline: glycylcycline derivative of minocycline

- Similar to tetracycline in mechanism of action & adverse effects (structurally similar).
- A broad spectrum of action include MRSA strains and vancomycin (VRE strains), beta-lactamase–producing Gram-negative bacteria, anaerobes, chlamydiae, and mycobacteria.
- Given by slow iv infusion (adjust dose in liver impairment).
- Used in complicated skin infection, intra-abdominal infections, and community acquired pneumonia.

❖ Advantages of doxycycline

1. Highly potent and has a longer duration of action (t1/2–24 h).
2. Can be administered orally, as well as intravenously
3. Completely absorbed after oral administration
4. Food does not interfere with its absorption
5. Incidence of diarrhea is rare (not affect the intestinal flora)
6. Can be safely given to Pts with renal failure (excreted primarily in bile)

❖ Adverse reactions

1. **G.I.T. irritation**: Nausea, vomiting, epigastric pain & diarrhea, and esophageal ulcerations.

2. **Inhibit intestinal flora** →Vit B & K deficiency
   → Superinfection (Pseudomembranous colitis →Treat by Oral Vancomycin or Metronidazole).

3. **Teratogenicity**

4. **Allergy:** Phototoxicity (sensitivity of skin to sunlight) with demeclocycline and tetracycline

Tetracyclines

4. **Teeth & Bone Abnormalities**: → taken during pregnancy & early childhood → Chelated by ca+2 & deposited in newly formed teeth & Bone →Teeth: yellow-brown discoloration.
→ Bone: Deformity & inhibition of growth.

5. **Hepatotoxicity (in renal failure or pregnancy).**

6. **Fanconi syndrome**: renal tubular dysfunction without dated tetracyclines (expired) except doxycycline causes nephrotoxicity (glucosuria, aminoaciduria, polyuria, proteinuria).

7. Doxycycline and minocycline causes Vestibular disturbances as dizziness and vertigo.

9. Demeclocycline causes nephrogenic diabetes insipidus.

10. Pseudotumour cerebri (rare)

❖ Contraindications:

- Renal impaired patients (except doxycycline).
- Pregnant, and breast-feeding women (category D).
- Children up to the age of 8 years

Chloramphenicol

3. Chloramphenicol: 250 mg caps – 100 mg I.V

- It is a broad spectrum, **bacteriostatic** antibiotic with high tissue penetration.
- It is derived from fungus (Streptomyces Venezuelae).

❖ Pharmacokinetics:

- Given orally, parenterally and topical.
- Distributed to all tissues (BBB, placental barrier) and cone in, eye, Milk & Bile.
- Metabolized in liver, inhibits the HME.
- excreted mainly in urine.

▪ Mechanism of action:

- It binds reversibly to the 50S subunit → inhibits peptidyl transferase → Prevents the formation of peptide bond → inhibition of protein synthesis.

- Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria → inhibit mitochondrial protein synthesis in mammalian cells → **bone marrow toxicity**

Chloramphenicol

❖ Antibacterial spectrum: .

- Broad spectrum including anaerobes
  - **Gram +ve cocci & bacilli**: very weak due to development of resistance
  - **Gram-ve cocci**: active against Neisseria meningitis , Moraxella.
  - **Gram –ve bacilli**: In respiratory tract (H. influenza) & Urinary tract (E.coli), small intestine (Salmonella typhi ,vibrio cholera ,Yersinia), Large intestine (Shigella) .
  - Not active against Pseudomonas
- Active against **anaerobes & Atypical bacteria**: Rickettsia , Chlamydia , mycoplasma

- It is **bacteriostatic** agent, but at high concentration, it can be **bactericidal** against H. influenzae N. meningitides, S. pneumoniae, Salmonella typhi and Bacteroides species..

❖ Resistance

- Production of inactivating enzyme → **acetyltransferase**,
- Decreased permeability of the microbial cell wall.
- Ribosomal mutation.

Chloramphenicol

❖ **Therapeutic Uses :** as eye ointment or drops & I.V.

- Because of its toxicity, its use is restricted to life-threatening infections

1) **Typhoid & Paratyphoid fever** (3rd gene cephalosporin & fluoroquinolones are best).

2) **Bacterial meningitis:** caused by H. influenzae, N. meningitidis and S. pneumoniae. (ADD Ampicillin). (3rd cephalosporin are drug of choice)

3) **Rickettsial infections**: (Tetracycline are the best)

4) **Anaerobic infections:** used in combination with metronidazole for the treatment of brain, lung, intra-abdominal or pelvic abscesses. 2nd choice

5) **Topically** in eye and ear infections.

Chloramphenicol

❖ **Adverse effects**: Pregnancy: category C

.1. **Bone marrow suppression**: may be dose-dependent (as hemolytic anemia, leukopenia and thrombocytopenia) or idiosyncratic (aplastic anemia)

2. Gray Baby Syndrome: in newborn due to undeveloped liver & kidney function → High drug levels accumulate → severe vomiting , hypotension ,cardiovascular collapse, cyanosis (gray skin)

3. GIT upset & superinfections (candidiasis).

4. **Enzyme inhibitor:** ↑ warfarin, phenytoin & oral hypoglycemics level.

4. Macrolides

❖ Preparations:

- **Short acting:** Limited tissue diffusion . Erythromycin 250 mg/6 hours orally.
- **Intermediate acting**: High tissue diffusion .Roxithromycin &clarithromycin /12 hours. (semisynthetic from Erythromycin)
- **Long acting**: Very high tissue diffusion : Azithromycin 500 mg once daily. (semisynthetic from Erythromycin)

❖ Mechanism of action: (Bacteriostatic)

- Macrolides bind to 50 S ribosomal and inhibit translocation of amino acids → inhibiting protein synthesis. **streptogramin**s and **lincosamide** have same M.O.A
- Macrolides are **bacteriostatic** but at higher concentrations can be **bactericidal**

Macrolides

❖ Resistance:

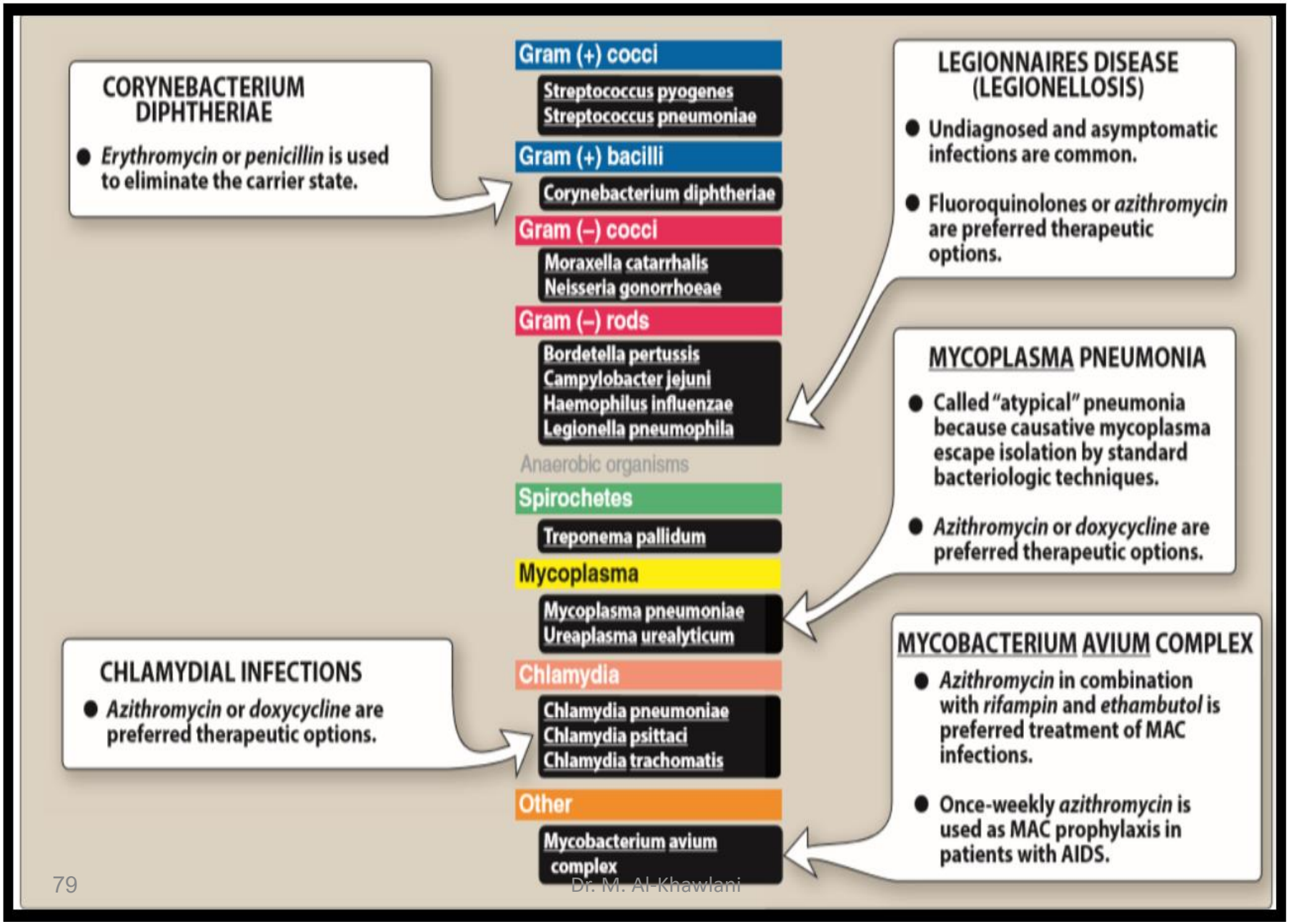
1. Presence of efflux pumps
2. Production of **esterase enzyme** in gram-negative bacteria
3. **Ribosomal protection (**ribosomal binding site) by chromosomal mutation or by the production of a methylase (adds a methyl group to the ribosomal binding site (in G+ve bacteria)

NB: streptogramins and lincosamide share the same ribosomal binding site → cross resistance with macrolides

❖ Spectrum:

- **Gram +ve cocci**: Strept., staph. & pneumococci.
- **Gram +ve bacilli** : corynebacterium diphthriae.
- **Gram -ve cocci**: Gonorrhea.
- **Some Grame -ve bacilli**: Helicobacter, H. influenza, B. pertussis & Legionella.
- Mycoplasma pneumoniae, Chlamydia, and Spirochaetes.

Macrolides


CORYNEBACTERIUM DIPHTHERIAE
Erythromycin or penicillin is used to eliminate the carrier state.
Gram (+) cocci
Streptococcus pyogenes
Streptococcus pneumoniae
Gram (+) bacilli
Corynebacterium diphtheriae
Gram (–) cocci
Moraxella catarrhalis
Neisseria gonorrhoeae
Gram (–) rods
Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila
Anaerobic organisms
Spirochetes
Treponema pallidum
Mycoplasma
Mycoplasma pneumoniae
Ureaplasma urealyticum
Chlamydia
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
Other
Mycobacterium avium complex
LEGIONNAIRES DISEASE (LEGIONELLOSIS)
Undiagnosed and asymptomatic infections are common.
Fluoroquinolones or azithromycin are preferred therapeutic options.
MYCOPLASMA PNEUMONIA
Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
Azithromycin or doxycycline are preferred therapeutic options.
CHLAMYDIAL INFECTIONS
Azithromycin or doxycycline are preferred therapeutic options.
MYCOBACTERIUM AVIUM COMPLEX
Azithromycin in combination with rifampin and ethambutol is preferred treatment of MAC infections.
Once-weekly azithromycin is used as MAC prophylaxis in patients with AIDS.

Macrolides

❖ Pharmacokinetics:

- Erythromycin is destroyed by gastric acidity, so given as enteric-coated tablets, Stable salts or esters (erythromycin estolate and erythromycin stearate)
  - clarithromycin and azithromycin are acid stable and can be given orally.

- Food interferes with the absorption of erythromycin and azithromycin.

- They are widely distributed in the tissues except CSF. Passes placental barrier and are safe in pregnancy

- Azithromycin is concentrated in neutrophils, macrophages and lung tissue, so they have long t1/2 (given once daily) and they are useful against intracellular organisms.

- Erythromycin and azithromycin are primarily concentrated and excreted in the bile.

- clarithromycin eliminated by the kidney as well as the liver. The dosage of this drug should be adjusted in patients with renal impairment.

- Advantages of clarithromycin & azithromycin over erythromycin:
  - Gastric acid stability. Better absorption, Long t1/2
  - Not HME inhibitor (azithromycin).

	Erythromycin	Clarithromycin	Azithromycin	Roxithromycin
1. Source	Natural	Semisynthetic	Semisynthetic	Semisynthetic
2. Duration of action	Short acting (6 h)	Intermediate acting (12h)	Long acting	Intermediate acting
3. GI absorption	Incomplete,	Good, but undergoes first-pass metabolism	Good	Good
4. Acid labile/ stable	Acid labile, hence administered as enteric coated tablets or esterified forms	Acid stable	Acid stabile	Acid stable
5. Antibacterial spectrum and therapeutic uses	Narrow spectrum Uses Erythromycin has similar to penicillin G + Resistant to B-lactamase	Expanded spectrum—effective against Mycobacterium avium complex (MAC), Chlamydia, Legionella, Moraxella, Toxoplasma gondii, and H influenzae and H. pylori,	▪ Less effective on Gm+ve, more effective on Gm-ve than erythromycin. ▪ Potent against Chlamydia. ▪ effective against MAC, H. influenzae, T. gondii,	Almost similar to erythromycin
6. Dosage and duration of therapy	250–500 mg oral QID for 7 days. Orally, IV.	250 -500 mg BD for 1–2 week	500 mg OD 1 h before or 2 h after food for 3–5 days	150 mg BD half-an-hour before food for 7 days
7. Enzyme inhibitor (HME)	Yes, causes various drug interactions	Yes, drug interactions are same as erythromycin	No, drug interactions are rare	No, drug interactions are rare

❖ Therapeutic Uses of Macrolides

1. As a drug of choice in the following conditions:

- **Mycoplasma pneumoniae infections**: Azithromycin and clarithromycin are often used for the treatment of community-acquired pneumonia. Erythromycin can also be used.
- **Legionnaires' pneumonia**: azithromycin,
- **Chlamydial infections**: azithromycin, for chlamydial infections in children and pregnant women.
- **Diphtheria:** Erythromycin
- **Pertussis (whooping cough)**: Erythromycin is most effective for the treatment as well as for prophylaxis of close contacts. Clarithromycin and azithromycin are also effective.

❖ Therapeutic Uses of Macrolides

2. As an alternative drug:

- **Prophylactic uses:**
  - **Alternative to penicillin in penicillin-allergic:** prophylaxis in rheumatic fever and dental procedures to avoid bacterial endocarditis, azithromycin (500 mg PO 1 h before the procedure) can be used.
- **Tetanus:** A course of oral erythromycin for 10 days may be given to eradicate C. tetani.
- **Tonsillitis, pharyngitis, otitis media, pneumonia:** (H. influenza & Streptococcal Moraxella infections: azithromycin and erythromycin.
- **Erythromycin acts as prokinetic** in cases of diabetic gastroparesis by stimulating motilin receptors in GIT.
- **Used to eradicate H. pylori** in pts with Peptic ulcer disease (clarithromycin)
- **Treatment of sexually transmitted diseases** (2nd choice) : gonorrhea and syphilis.

Macrolides

❖ Adverse effects:

- **GIT disturbances**: anorexia, nausea, vomiting, epigastric pain, colic and diarrhea. Erythromycin > Others
- **Cholestatic hepatitis** (jaundice) caused by estolate ester when drug therapy lasts longer than 10 days or repeated courses are prescribed.
- **Allergic reactions**: fever, rash, and eosinophilia.
- **Drug interactions**: Erythromycin & clarithromycin inhibit liver microsomal enzymes → ↓ hepatic metabolism of other drugs (as theophylline, cyclosporins, digoxin. warfarin) → ↑ toxicity of these drugs.

Contraindications: liver diseases

NB:

- Azithromycin & Erythromycin: they don't need dose adjustment in renal dysfunction.
- Combination of the therapeutic dose of erythromycin with penicillin antagonizes the bactericidal effect of penicillin

4. Spiramycin

- Similar macrolide antibiotic, as erythromycin in spectrum of activity & properties.
- Used in oral cavity infection
- Specific utility for Toxoplasmosis and recurrent abortion in pregnant women
- **Side effects:** gastric irritation, nausea, diarrhoea and rashes.

5. **Ketolides**: Telithromycin: 800 mg/day for 5-10 days orally).

- Semi-synthetic macrolide.
- Given orally once daily due to high tissue concentration.
- Similar mechanism & spectrum to Erythromycin.
- Telithromycin may be effective against macrolide- resistant organisms.
- **Used** mainly in respiratory tract infection e.g.community-acquired pneumonia .
- HME inhibitor
- **Adverse effects**: hepatic dysfunction and prolongation of the QTc interval

5. Lincosamines:

❖ **Preparation:** Clindamycin & Lincomycin

- Clindamycin is semisynthetic derivative of lincomycin, and is more potent than lincomycin

1- Clindamycin

- They are narrow spectrum antibiotics with high tissue penetration, concentrated in bone.
- They act at the same site with macrolides, binding to 50S subunit →↓ aminoacyl translocation →↓ inhibits protein synthesis. (**bacteriostatic**)

- Their spectrum of activity is restricted to gram +ve organisms(cocci and bacilli, MRSA) .all anaerobes except C.difficle , atypical organisms (mycoplasma) , toxoplasmosis, pneumocystitis carinii (2nd choice).

- It is used specifically against anaerobic infections.

- Absorbed orally (not affected by food) and can be given IM, IV and topically.
- Resistance mechanisms are the same erythromycin, and cross-resistance with macrolide

Lincosamines

❖ Clinical Use

1) **Treatment of anaerobic infections (DOC):** as dental infections, lung abscess, anaerobic lung and other abscesses

2) **Prophylaxis against endocarditis**. before dental procedures in Pts allergic to penicillins

3) It is used in bone infection, Osteomyelitis (good penetration into bone).

4) **Treatment of Pneumocystis carinii pneumonia** in combined with **primaquine** as alternative to Co-trimoxazole.

- It is also used in combination with pyrimethamine for AIDS- related toxoplasmosis of the brain (drug of choice).

❖ Adverse Effects

- **Pseudomembranous colitis** (superinfection)— diarrhoea with blood and mucus in the stools due to Clostridium diffcile. (treated with metronidazole or vancomycin)

- **Impaired liver functions**.
- **Allergy**: skin rash.

NB: Pregnancy: category B

6. Streptogramins:

❖ Preparation: Quinupristin/Dalfopristin

- Quinupristin/dalfopristin is a mixture of two streptogramins in a ratio of 30 to 70, respectively.
- Due to significant adverse effects, the drug is used for the treatment of severe vancomycin-resistant Enterococcus faecium (VRE) in the absence of other therapeutic options.

❖ Pharmacokinetics

- The drugs are not absorbed orally .They are widely distributed after IV administration
- Both compounds undergo hepatic metabolism, with excretion mainly in the feces.
- Potent HME inhibitors → drug interaction.

❖ Mechanism of action

- The streptogramins share the same ribosomal binding site as the macrolides and clindamycin and thus inhibit protein synthesis in an identical manner (50S subunit of bacterial ribosomes)

- It is **bactericidal against:** Gram-positive cocci, including multidrug-resistant strains of streptococci, penicillin resistant strains of S pneumoniae, methicillin-susceptible and resistant strains of staphylococci (MRSA), and E faecium VRE.

Streptogramins

❖ Resistance:

- Like macrolide, modification of the quinupristin binding site (methylates). Enzymatic inactivation of dalfopristin (acetyltransferase), or efflux pump can also decrease levels of the antibiotics in bacteria.

❖ Therapeutic uses

- Treatment of Serious infections caused by staphylococci,MRSA or by vancomycin-resistant Enterococcus faecium (VRE),

❖ Adverse effects

- Pain and phlebitis at the infusion site
- Arthralgias and myalgias (more common in pts with hepatic insufficiency) →↓ dosing frequency from every 8 h to every 12 h.
- Hyperbilirubinemia due to competition with the antibiotic excretion.
- Enzyme inhibitor → drug interactions (similar to erythromycin)

F. Oxazolidinones

❖ Preparation: linezolid; 600 mg /12h oral/ IV

- Bacteriostatic , narrow spectrum antibiotic
- 100% GIT absorption, administered by oral and IV infusion
- Very wide distribution to all tissues of the body including brain and respiratory mucous , ischemic tissues (diabetic foot), inside the eye.
- It is metabolized in the liver to inactive compounds.
- It is excreted in urine and in feces as oxidation products (not necessary adjustment dose in renal or hepatic failure).

❖ Mechanism of Action

- Linezolid binds to a unique site located on the 23S of the 50S subunit, → inhibiting the initiation complex → Inhibits protein synthesis
- No cross-resistance with other protein synthesis inhibitors.

- Resistance is caused by mutation of the linezolid binding site on 23S ribosomal RNA.

Oxazolidinones

❖ Antibacterial Spectrum

- G+ve bacteria: streptococci, staph, enterococci. including MRSA, VRSA, VRE, corynebacteria, and L monocytogenes.
- Active against Mycobacterium tuberculosis.
- It is primarily a **bacteriostatic** agent but is **bactericidal** against streptococci.

❖ Therapeutic uses

- Treatment of VRSA, VRE, and drug-resistant pneumococci
- Uncomplicated and complicated skin & skin structure infection (SSTIs) caused by susceptible gram-positive bacteria
- Treatment of multidrug-resistant tuberculosis and Nocardia infections

❖ Adverse effects

- **GI side effects** — nausea, vomiting and diarrhea.
- **Bone marrow suppression**: including anemia, neutropenia, pancytopenia, and thrombocytopenia (if use >10 day).
- **Peripheral and optic neuropathy after prolonged use** → reverse upon drug discontinuation. (if use >24 day).
- Rash, pruritus, headache, oral/vaginal candidiasis (occasionally).

Nucleic acid synthesis Inhibitors

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

DNA Gyrase inhibitors (Quinolones & fluoroquinolones)

Quinolones and fluoroquinolones

❖ Preparation:

❑ Quinolones:

- **First generation:** Nalidixic acid.
- Nonfluorinated, Narrow spectrum with low tissue penetration
- Not used in systemic infections → insufficient plasma cone. (not achieve systemic antibacterial levels) → Was used only in uncomplicated UTIs with G-ve bacilli.
- Rapid resistance limits its use.

❑ Fluoroquinolones (FQs)

- **Second gen.**, FQs): Ciprofloxacin, Norfloxacin, Ofloxacin, Pefloxacin and Lomefloxacin
- **Third gen.** FQs; : Levofloxacin, Gatifloxacin
- **Fourth gen.** FQs : Moxifloxacin

- Synthetic fluorinated analogues of nalidixic acid
- Broad spectrum with high tissue penetration → Achieve bactericidal levels in blood and tissues → used in systemic infections

N.B.: Norfloxacin is used in urinary tract infections only as it does not achieve systemic levels.

Quinolones and fluoroquinolones

❖ Pharmacokinetics:

- Absorbed orally (↓ by food and drugs containing Fe+2 &, Mg+2 & Al+3
- Given also IV, topically or as eye drops & ointments.

- Widely distributed into body fluids and tissues, reaches high concentration in bone, urine (except moxifloxacin), lungs, prostatic tissue, intracellularly macrophages → Useful against intracellular organisms such as TB, Chlamydia, Mycoplasma. .
- Metabolized by liver.
- It is excreted mainly in urine except moxifloxacin by biliary excretion.
- Cross placenta & excreted with milk.
- Serum t½: 3-10 h, but levofloxacin, Gemifloxacin, gatifloxacin, and moxifloxacin have long half-lives → once-daily dosing.

❖ Mechanism of action: **bactericidal**

- Inhibit DNA gyrase (topoisomerase II) enzyme, which is responsible for unwinding of double-stranded DNA in gm-ve organisms → inhibition of DNA replication.
- Also inhibits topoisomerase IV in gm+ve organisms responsible for cell division →↓ DNA Replication

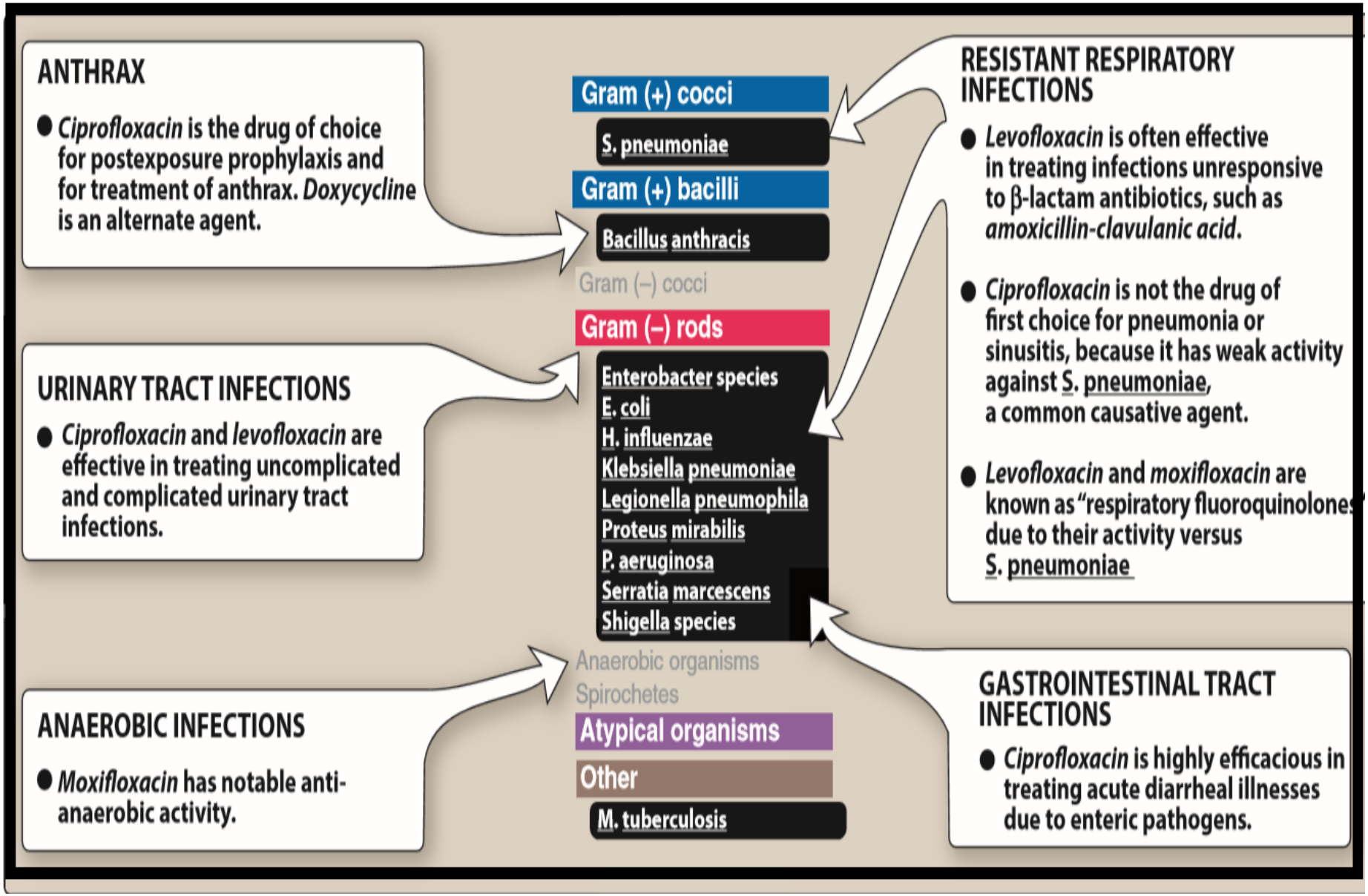
- Fluoroquinolones exhibit postantibiotic effects and concentration dependent killing.

Quinolones and fluoroquinolones

Generation	Spectrum of activity	Drugs
First Gen	• Moderate G-ve activity • Not achieve systemic antibacterial level. • Restricted to the treatment of uncomplicated UTI	Nalidixic acid (quinolone)
Second Gen.	• Expanded against aerobic G-ve organisms: pseudomonas, E.coli, H. influenza, proteus, salmonella • Moderate activity against G+ve: staph (not MRSA), weak on strep & pneumo-cocci. • Active against atypical organisms: Mycoplasma, Chlamydia and Legionella • inactive against Strept. and anaerobes	• Ciprofloxacin • Norfloxacin • Lomefloxacin • Ofloxacin • Pefloxacin
Third Gen	• Extended G-ve activity • Improved activity specific G+ve bacteria (Strept. pneumoniae and some staph). • Active against atypical organisms	• Levofloxacin • Gatifloxacin
Fourth Gen.	• Improved G+ve coverage • Maintains G-ve activity, weak on pseudomonas • Active against anaerobic	Moxifloxacin

- Ciprofloxacin (The best) and Levofloxacin are the most active agent against, P aeruginosa.
- Moxifloxacin (The best),and Levofloxacin, have improved activity against G+ve cocci such as S. pneumoniae so-called respiratory FQs.

Quinolones and fluoroquinolones


ANTHRAX
● *Ciprofloxacin* is the drug of choice for postexposure prophylaxis and for treatment of anthrax. *Doxycycline* is an alternate agent.
URINARY TRACT INFECTIONS
● *Ciprofloxacin* and *levofloxacin* are effective in treating uncomplicated and complicated urinary tract infections.
ANAEROBIC INFECTIONS
● *Moxifloxacin* has notable anti-anaerobic activity.
Gram (+) cocci
S. pneumoniae
Gram (+) bacilli
Bacillus anthracis
Gram (–) cocci
Gram (–) rods
Enterobacter species
E. coli
H. influenzae
Klebsiella pneumoniae
Legionella pneumophila
Proteus mirabilis
P. aeruginosa
Serratia marcescens
Shigella species
Anaerobic organisms
Spirochetes
Atypical organisms
Other
M. tuberculosis
RESISTANT RESPIRATORY INFECTIONS
● *Levofloxacin* is often effective in treating infections unresponsive to β-lactam antibiotics, such as *amoxicillin-clavulanic acid*.
● *Ciprofloxacin* is not the drug of first choice for pneumonia or sinusitis, because it has weak activity against S. pneumoniae, a common causative agent.
● *Levofloxacin* and *moxifloxacin* are known as "respiratory fluoroquinolones" due to their activity versus S. pneumoniae
GASTROINTESTINAL TRACT INFECTIONS
● *Ciprofloxacin* is highly efficacious in treating acute diarrheal illnesses due to enteric pathogens.

❖ Therapeutic uses:

1)Urinary Tract Infections (UTIs)

- Norfloxacin complicated and uncomplicated UTIs.
- Ciprofloxacin, and levofloxacin are also used for UTIs.

2) Prostatitis

- Ciprofloxacin, levofloxacin and ofloxacin **(1st choice)**

3) Sexually Transmitted Diseases (STDs): (Chlamydia , gonorrhea).
Ofloxacin and levofloxacin **(2nd choice)**

4) Gastrointestinal and infective diarrhea & Traveler`s diarrhea : shigella, salmonella, E coli, and campylobacter

- Ciprofloxacin, and ofloxacin → shigellosis
- Norfloxacin→↓ the duration of diarrhea in cholera

5) Typhoid fever :

- Ciprofloxacin: **(1st choice),** Multidrug-resistant cases are treated with ceftriaxone.

- Localized abscess, intra abdominal infection: (Active against anerobes): moxifloxacin:

Quinolones and fluoroquinolones

6) Bone, Joint, skin and Soft Tissue Infections

7) Respiratory Tract Infections: resistant to B-lactams & atypical pneumonia due to chlamydia, mycoplasma, legionella, Levofloxacin, and moxifloxacin, used for Upper RT & Lower RT infections (community-acquired pneumonia (CAP), and nosocomial pneumonia).

8) Tuberculosis:

- Ciprofloxacin, levofloxacin, or moxifloxacin: used as a component of chemotherapy against multidrug-resistant tuberculosis

9) Anthrax

- Ciprofloxacin **(1st choice)** for prophylaxis and treatment of anthrax (caused by Bacillus anthracis) .

Quinolones and fluoroquinolones

❖ Adverse reactions

1) Inhibition of protein synthesis in bones , cartilage damage (**Arthropathy**), → avoid in pregnant and lactation and in children under18 years of age.

2) **Gut upsets**: nausea, vomiting, and diarrhea (Superinfections) (Lomefloxacin, ciprofloxacin and levofloxacin)
3) **CNS disturbances**: headache, dizziness, insomnia and seizures.

4) **Hypersensitivity** & **photosensitivity** (esp. with lomefloxacin and pefloxacin): rash, itching, urticaria, swelling of lips → use sun-screen & sun-blocks.

5) Newer fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin) prolong the QTc interval.

6) Gatifloxacin changes in blood glucose level (hypoglycemia & hyperglycemia,

❖ Contraindications

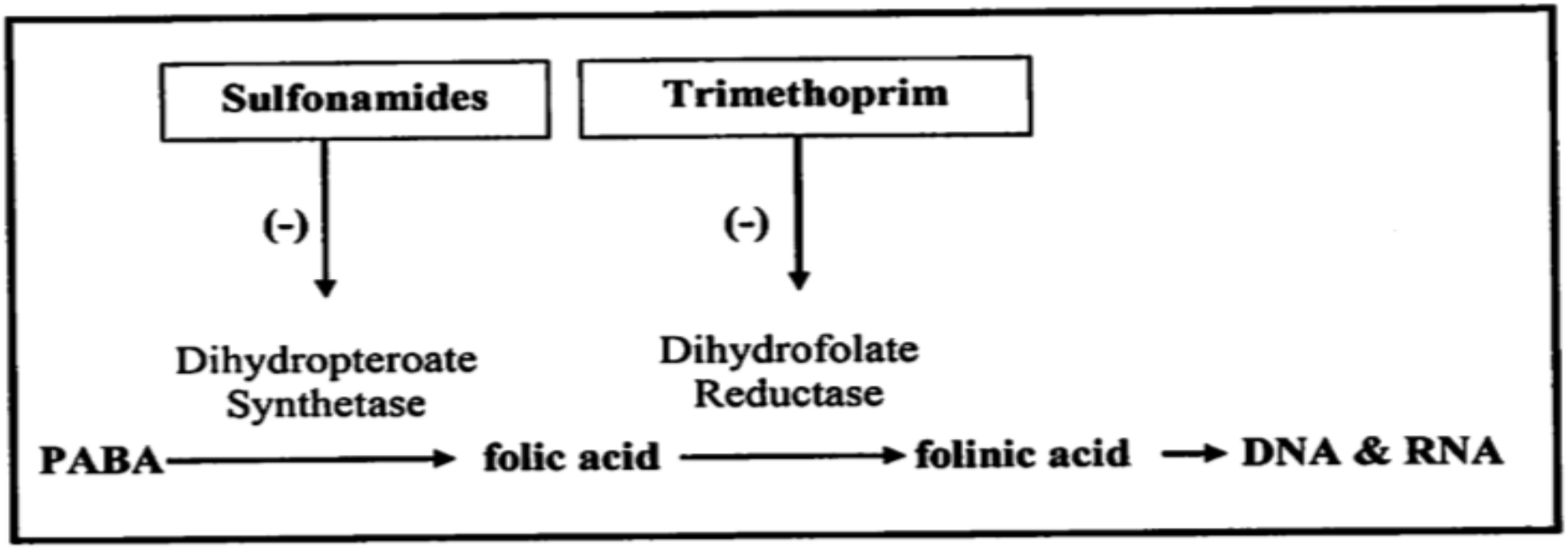
- Pregnancy and lactation - children under18 years.
- Patients predisposed to arrhythmia - Epileptic patients.
- Gatifloxacin, contraindication in diabetic pts)

❖ Drug interactions:

- Antacids, sucralfate and iron salts →↓ absorption of fluoroquinolones.
- Ciprofloxacin, norfloxacin, pefloxacin and ofloxacin → HME inhibitors →↓ metabolism of theophylline, caffeine, sulfonylurea and warfarin →↑ their serum levels→↑ their toxicity.
- NSADs potentiate the CNS side effects of FQs: headache, dizziness, and seizures (by augment displacement of GABA from its receptors by the FQs)

ANTIFOLATE DRUG
Sulfonamide & Trimethoprim

Antifolate drugs



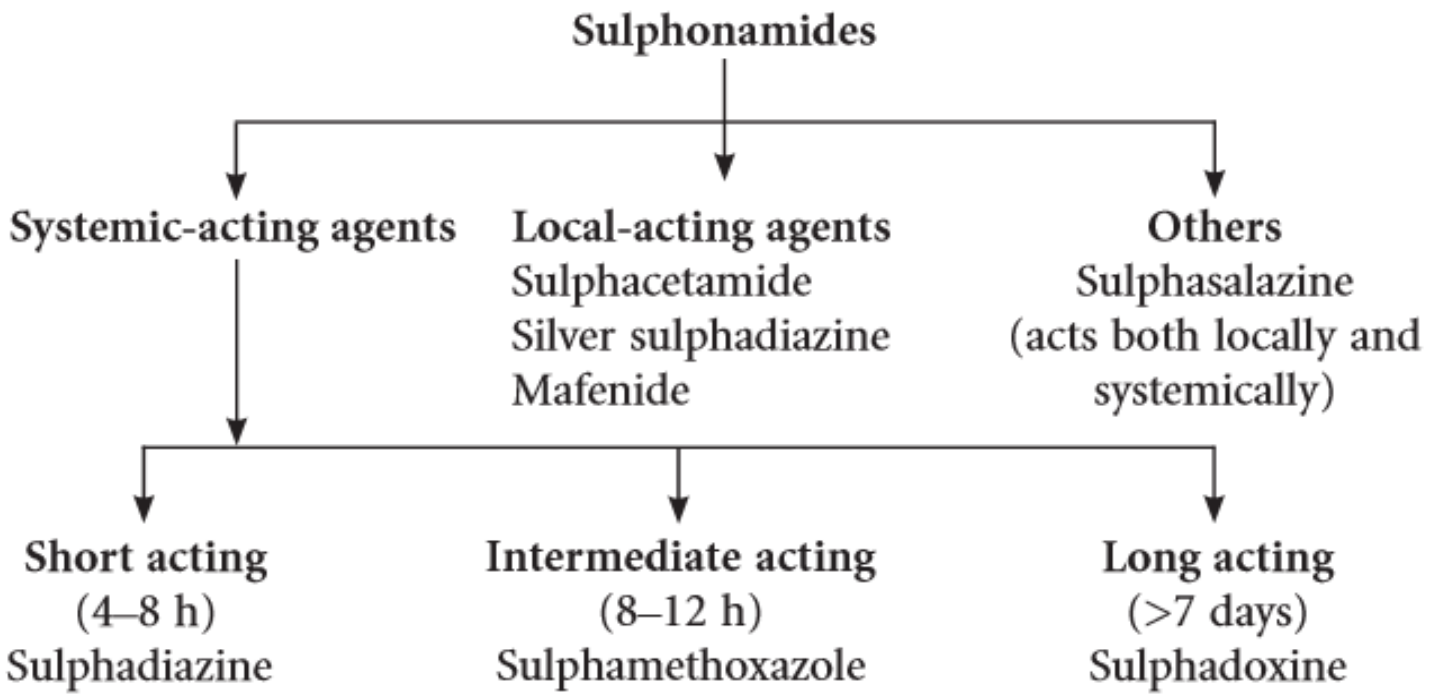
- Sulfonamides inhibit synthesis of folic acid by inhibition dihydropteroate synthetase enzyme
- trimethoprim and pyrimethamine inhibit activation of folic acid by inhibition of folate reductase enzyme

- Combining the sulfonamide (sulfamethoxazole) with trimethoprim → cotrimoxazole → a synergistic combination.

- It is **bactericidal** if combined with trimethoprim (cotrimoxazole).

Antifolate drugs

1. Sulfonamides:



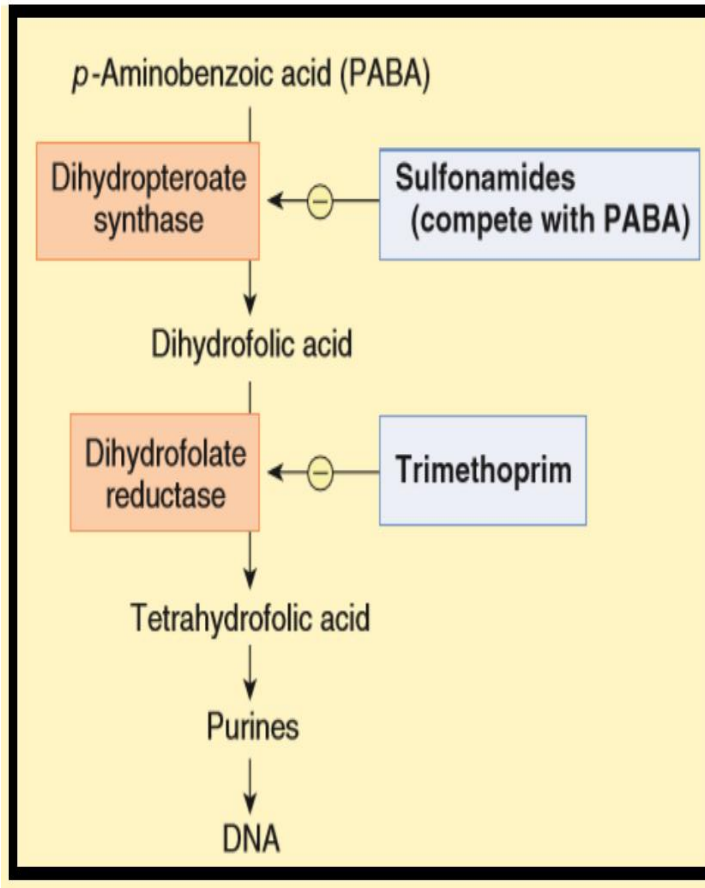
❖ Pharmacokinetics

- Some of them are well absorbed from GIT as systemic agents but some are poorly absorbed as sulfacetamide.
- Bound to plasma proteins → displacement of bilirubin & other drugs → hyperbilirubinemia jaundice, and Kernicterus (if given in late pregnancy & in neonates)
- Metabolized in liver mainly by acetylation.
- Excreted partly unchanged in urine

Antifolate drugs

❖ Mechanism of action of Sulphonamides: bacteriostatic

- Compete with bacterial PABA (due to structural similarity) for bacterial dihydropteroate synthetase → inhibition of folic acid synthesis



❖ Resistance to sulphonamides

- Resistance to sulphonamides. It could be due to:
  1. Overproduction of PABA.
  2. drugs that release PABA as Procaine
  3. Decreased sensitivity of DHPS to sulfa

❖ Spectrum:

- **Broad spectrum: Gm +ve & -ve bacteria** (NOT Pseudomonas or Proteus).
- **Now many strains** (Staph, Strept, Pneuma, Meningo & Gonococci) → Resistant
- **Atypical organism**: Chlamydia trachomatis, Nocardia.
- **Some protozoa :** malaria , toxoplasmosis, Pneumocystis carnii.

❖ Therapeutic Uses of Sulfa

A. Systemic Agents (Oral Absorbable)

- Sulfisoxazole (1 g/ 4 times daily) or sulfamethoxazole(1g/2-3 daily) are short- to medium-acting agents used almost exclusively to treat UTIs.
- Sulfamethoxazole + trimethoprim: used as antibacterial:
- Sulfadiazine + pyrimethamine for treatment of acute toxoplasmosis (**1st choice)..**
- Sulfadoxine + pyrimethamine (Fansidar), used as 2nd -line treatment and prophylaxis of malaria.
- Sulfisoxazole or Sulfadiazine used in treating infection due to Nocardia spp.

B. Local agent:

❑ Oral Non-absorbable Agents

- Sulphaguanidine: treat bacillary dysentery
- Sulphasalazine: Useful in Ulcerative colitis and inflammatory bowel disease .

Antifolate drugs

❑ Topical Agents

- Sulphacetamide: in ocular chlamydial infection (Eye infection)
- Silver Sulphadiazine: in burn infections, ointment (preferred to mafenide).
- Mafenide: in wound infections, ointment

❖ Side effects:

1. **Crystalluria:**
   Sulfonamides metabolites formed in liver precipitate in acidic urine → crystalluria & nephritis (avoid by↑ fluid intake & urine alkalinization by sodium bicarbonate).

2. **Hypersensitivity reactions:** skin rashes, itching, fever ,photosensitivity, Stevens–Johnson syndrome (rarely)

3. **Acute hemolytic anemia** in patients with G-6-Pd deficiency **and** Bone marrow depression (leucopenia or thrombocytopenia)

4. **Kernicterus** (Jaundice & CNS affection).

Antifolate drugs

❖ **Contraindications:**

- Newborns and infants less than 2 months of age
- In pregnant (especially, Last 2 weeks) and lactation.
- Allergy to sulfonamides. (cross allergy with thiazides and loop diuretics and sulphonylureas (oral hypoglycemics}.
- Favism.

❖ **Drug interactions**:

- ↑ action of warfarin, phenytoin and methotrexate. (by displacement from albumin binding sites)

Antifolate drugs

2-Trimethoprim: bacteriostatic

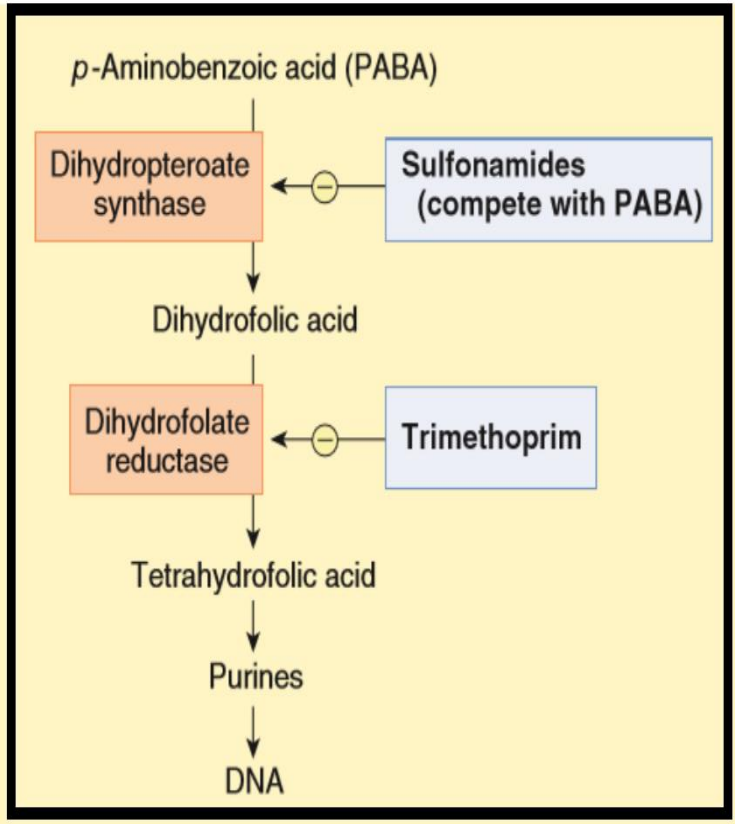
- **M.O.A:** Inhibits dihydrofolate reductase and inhibits synthesis of tetrahydrofolic acid (folinic acid) which is essential for DNA synthesis.

- Absorbed orally. Bound to plasma proteins. Concentrated in prostate and vaginal fluid. Excreted in urine and is intermediate acting

- **Used:** alone in UTIs and in bacterial prostatitis (although fluoroquinolones are preferred).

❖ **Adverse effects**:

- **Megaloblastic anemia** (folate deficiency).
- **leukopenia, and granulocytopenia**,



3- Co-Trimoxazole (Septrin)®

- Combination of Sulphamethoxazole (400 mg) + Trimethoprim (80 mg).

- **M.O.A:**
  - Sulphamethoxazole inhibits folate synthetase whereas trimethoprim inhibits folate reductase enzyme → **sequential blockade** (interfere with two successive steps in the same metabolic pathway) → supra-additive effect **bactericidal.**

- Given orally or by I.V infusion (twice daily) t½=10 hours.
- Distributed to all body fluids including CSF.

- **Advantages**

1. Synergistic combination. (bactericidal action, lower doses and decrease the resistance)
2. Less bacterial resistance than each drug alone.
3. More potent (Bactericidal) & wider-spectrum including Proteus, Salmonella, Shigella, H. influenza & Gonococcus.

Sulfonamides & trimethoprim

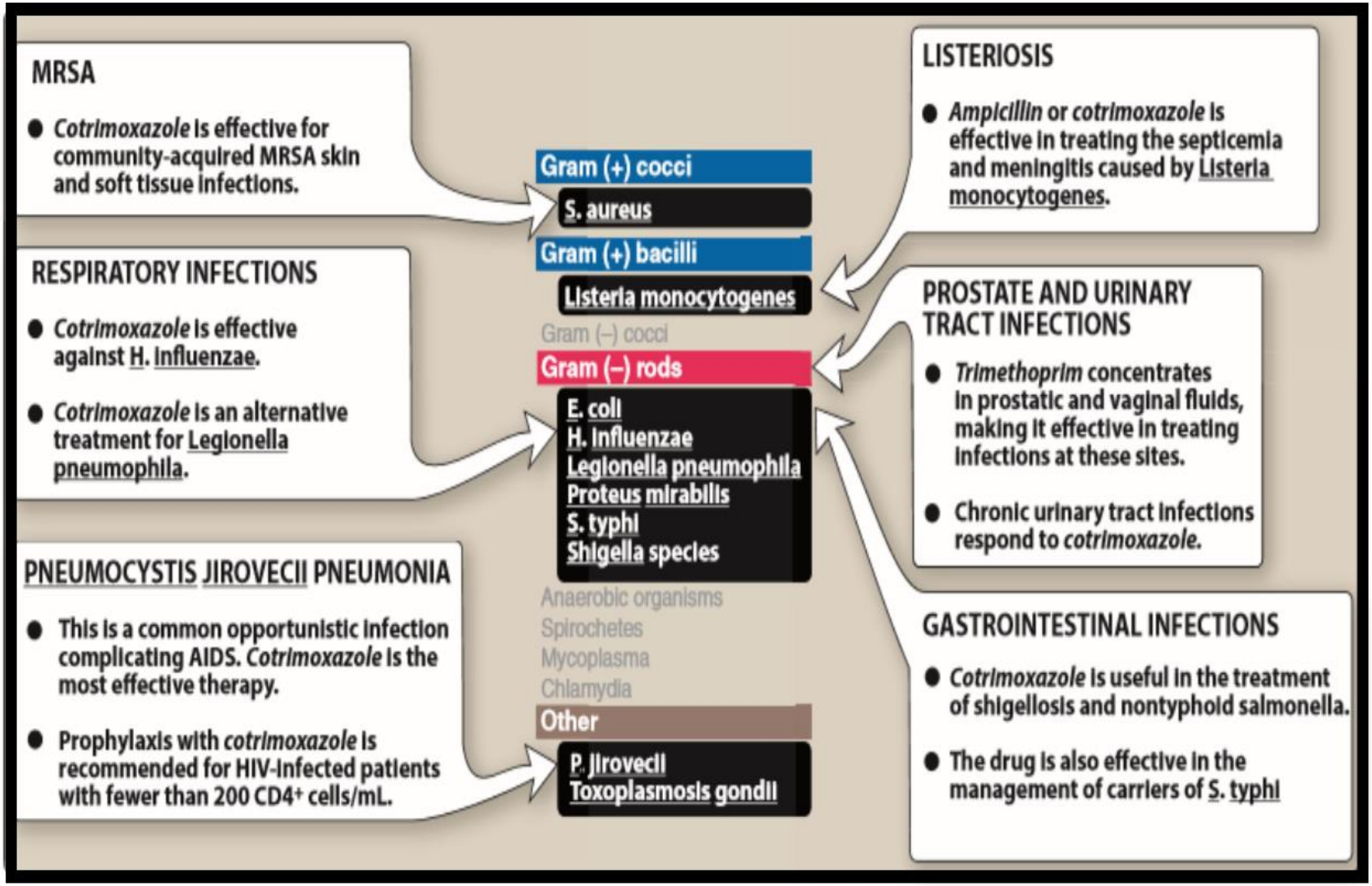
❑ Therapeutic Uses

- UTI, gonococcal urethritis and prostatitis.
- RTI: H. influenza & S. pneumonia
- In prophylaxis against Pneumocystis jirovecii pneumonia in immunosuppressed patient
- Gastroenteritis (traveler s diarrhea): Salmonella & Shigella infections.
- Typhoid fever (2nd choice).
- community-acquired skin and soft tissue infections (against MRSA).
- Nocardia species **(DOC)**

❑ Adverse effects

- Same as that of sulphonamides: skin rashes and gastrointestinal (GI) disturbances. nausea, vomiting, and stomatitis.
- **Megaloblastic anemia**
- **Bone marrow suppression** with leukopaenia, neutropaenia and thrombocytopaenia
- Cotrimoxazole is contraindicated in pregnancy (category D).

Sulfonamides & trimethoprim


MRSA
Cotrimoxazole is effective for community-acquired MRSA skin and soft tissue infections.
RESPIRATORY INFECTIONS
Cotrimoxazole is effective against H. influenzae.
Cotrimoxazole is an alternative treatment for Legionella pneumophila.
PNEUMOCYSTIS JIROVECII PNEUMONIA
This is a common opportunistic infection complicating AIDS. Cotrimoxazole is the most effective therapy.
Prophylaxis with cotrimoxazole is recommended for HIV-infected patients with fewer than 200 CD4+ cells/mL.
Gram (+) cocci
S. aureus
Gram (+) bacilli
Listeria monocytogenes
Gram (–) cocci
Gram (–) rods
E. coli
H. influenzae
Legionella pneumophila
Proteus mirabilis
S. typhi
Shigella species
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
P. jirovecii
Toxoplasmosis gondii
LISTERIOSIS
Ampicillin or cotrimoxazole is effective in treating the septicemia and meningitis caused by Listeria monocytogenes.
PROSTATE AND URINARY TRACT INFECTIONS
Trimethoprim concentrates in prostatic and vaginal fluids, making it effective in treating infections at these sites.
Chronic urinary tract infections respond to cotrimoxazole.
GASTROINTESTINAL INFECTIONS
Cotrimoxazole is useful in the treatment of shigellosis and nontyphoid salmonella.
The drug is also effective in the management of carriers of S. typhi

Typical therapeutic applications of cotrimoxazole (sulfamethoxazole + trimethoprim).

Anti-Mycobacterium drugs

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Anti-mycobacterium drugs

❑ Classification of Mycobacteria:

- Mycobacterium tuberculosis cause tuberculosis (TB).
- Mycobacterium leprae cause leprosy.

  - ➢ TB an acid-fast bacillus that grow slowly.
  - ➢ They can live extracellular, intracellular and necrotic tissue. that multiple slowly.

❖ Problems with TB therapy:

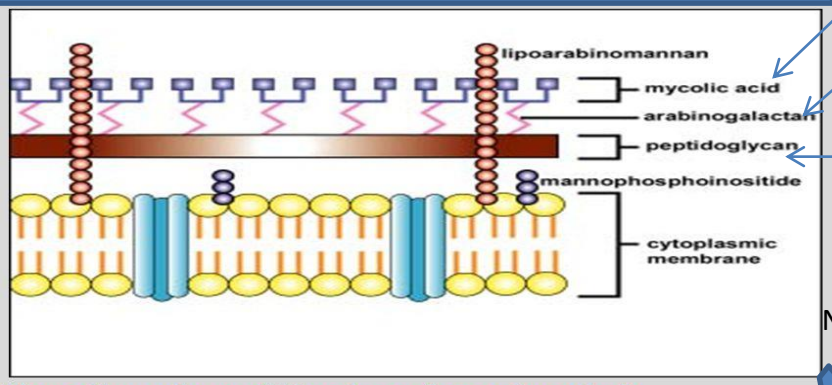
- The slow growth & intracellular location of mycobacteria
- Slowly growing → need a long therapy (minimum of 6 months up to 2years) to prevent relapse.
- TB can cause latent tuberculosis infection
- Resistant to most antibiotics and the response so combination of drugs is required.

❑ **Chemotherapy of mycobacterial** infections always involves the use of drug combinations

- Increase activity.
- Reduce the risk of resistance.
- Lower the dose and toxicity.

Mechanism of action of anti-tuberculous drugs

Inhibitors of cell wall



The cell envelope of *Mycobacterium tuberculosis.*

Mycolic acid synthesis inhibitors :INH , ethionamide ,pyrazinamide

Arabinoglycans synthesis inhibitors: ethambutol

Peptidoglycans inhibitors: carbenems , amoxacillin, cycloserine

Inhibitors of protein synthesis

Nucleic acids

Refampicin RNA polymerase inhibitor

RNA polymerase

Clofazimine inhibits mRNA binding to ribosome by binding to guanine base

mRNA

Inhibitors of mycobacterial cell division

Fluroquinolone is DNAgyrase inhibitor

DNA gyrase

DNA polymerase

Coiled circular DNA

DNA uncoiling

t RNA

mRNA

Termination codon

Peptide antibiotics block elongation of perptide chain

Uracil + Thymine

Tetrahydro-folic acid

Folic acid reductase

Folic acid (inactive

P-aminosalicylic acid inhibit folate reductase enzyme required for thymine synthesis

Inhibition of energy production

Bedaquiline inhibits ATP formation

❖ Anti-Tubercular drugs:

A) **First Line drugs (standard drugs): (**more effective and less toxic than 2nd line drugs).

1) Isoniazid: affects intracellular & extracellular organisms.
2) Rifampicin: affects organisms at all sites.
3) Pyrazinamide: affects intracellular organisms. (resistant strains).
4). Ethambutol: affects extracellular organisms (poor penetration through cell wall) .
5) Streptomycin: affects extracellular organisms

- **NB**: Isoniazid & Rifampicin are the most active drugs

b) **Second Line drugs (reserve drugs)** : (used in resistance to 1st line drugs) :

1) Para amino salicylic acid (PAS).
2) Ethionamide. → Peripheral &optic neuritis
3) Cycloserine. → Peripheral neuritis & CNS dysfunction
4) Aminoglycosides: kanamycin, amikacin, and capreomycin.
5) Fluoroquinolones. (ciprofloxacin, levofloxacin & moxifloxacin).
6) Bedaquiline

Anti- Tubercular drugs

1. Isoniazid: (lsonicotinic acid hydrazide = INH):

- It is orally effective, distributed well all over the body (CNS), affects against intracellular & extracellular organisms, metabolized in the liver by acetylation, excreted in urine
- It is a pro-drug activated by catalase–peroxidase enzyme within the mycobacteria
- Structurally similar of pyridoxine (Vitamin B6) → competition between vitamin B6 (pyridoxine) and INH → neuropathy
- **Spectrum:** Mycobacteria T.B. only.

❖ **Mechanism of action:** **Tuberculocidal** in growing and **static** in non growing mycobacteria..

➢ Inhibits catalase–peroxidase enzyme (essential for synthesis of mycolic acid) → inhibition of cell wall synthesis

❖ **Resistance:** occurs rapidly if it is used alone

- Mutations of the catalase-peroxidase and related enzymes responsible for activation of the pro-drug

NB: Cross resistance may occur between isoniazid and ethionamide.

Anti- Tubercular drugs

❖ Indications:

1. **First-line drug** for the treatment of active T.B. (in combination with rifampicin + pyrazinamide + ethambutol).

2. **As single agent** for treatment of latent tuberculosis or prophylaxis in unimmunized contact with patients (relatives and medical stuff).

❖ Adverse effects:

1. **Neurotoxicity** especially in slow acetylators (Vit B6 deficiency): peripheral neuritis, optic neuritis, memory impairment & convulsions (Should be prescribed vitamin B6 prophylactically with INH to decrease neuropathy).
2. **Hepatotoxicity:** risk is increased with age, (jaundice, and hepatitis).
3. **Hemolysis** is patients with G-6-PD deficiency (idiosyncrasy).
4. **Allergy:** rash, fever.

❖ Drug interaction:.

- INH → HME inhibitor → ↑ phenytoin, &carbamazepine serum level and toxicity.
- Al3+ -containing antacids → ↓ its absorption.

2. Rifamycins: Rifampin (rifampicin), rifabutin, rifapentine.

❖ Rifampin (rifampicin): has broader antimicrobial activity than isoniazid.

- It is given orally and is rapidly absorbed from the GI tract (affected by food).
- It is distributed widely to all tissues (BBB) &can reach TB cavities & sputum & penetrate macrophages, killing slowly growing TB bacilli inside.
- Metabolized by the liver (undergoes enterohepatic recirculation) → given once daily
- HME inducer → drug interaction
- Excreted: Feces - urine (causes orange-red discoloration of urine).

❖ **Mechanism of action**: bactericidal (tuberculocidal)

- inhibits DNA-dependent RNA polymerase leading to inhibition of RNA synthesis

❖ **Spectrum:**.

- Affects against TB at all sites & leprosy
- Potent broad spectrum bactericidal: Gram -ve bactertia as meningococci & Influenza, Brucellosis and Gram +ve bacteria as Staph (**osteomyelitis**).
- Chlamydia & legionella.
- Antiviral effect.

Anti- Tubercular drugs

❖ Indications:

1. **T.B treatment** (With other drugs) & **prophylaxis** (as a single drug, 2nd choice) for **latent tuberculosis.**
2. **Leprosy**.
3. **Prophylaxis** of meningococcal and H. influenzae meningitis **(DOC)**
4. **Treatment of osteomyelitis** and prosthetic valve endocarditis in combination with a B-lactam antibiotic or vancomycin
5. **Brucellosis**; plus doxycycline (1st choice).

❖ Adverse effects:

1. Cholestatic hepatitis and jaundice.
2. Flu-like syndrome at the start of treatment.
3. GIT disturbances.
4. Allergy: fever, rash, and blood dyscrasias (thrombocytopenia).
5. Orange-red discoloration of urine.

❖ Drug interaction:

- HME inducer → ↑ clearance of theophylline, warfarin, oral hypoglycemics, digitoxin, and oral contraceptives.

- **Resistance**: rapid (but no cross resistance with other anti-TB drugs).

3. Pyrazinamide.

- It is a synthetic analogue of nicotinamide.
- Absorbed orally- distributed to all tissues: inflamed meninges (CSF). Effective against intracellular bacilli. No effect on organisms in necrotic tissues
- Metabolized by the liver and excreted in urine and decreases uric acid excretion

❖ **The mechanism of action:** **Tuberculocidal** against resistant intracellular bacilli.

- It is converted to pyrazinoic acid (active form of the drug) by mycobacterial pyrazinamidase, present in M tuberculosis → inhibits mycobacterial mycolic acid biosynthesis.

❖ **Therapeutic uses:** In combination with INH and rifampin to minimize resistance (in initial therapy for 2 months).

❖ **Adverse effects**

- Hepatotoxicity.
- Hyperuricemia (gouty attacks)& arthralgia.

4. Ethambutol:.

- Absorbed orally- distributed to all tissues including inflamed meninges (BBB) -excreted in urine and decreases uric acid excretion.

❖ Mechanism of action: **Tuberculostatic**.

- Inhibition of arabinosyl transferase enzyme → Inhibition cell wall synthesis of mycobacteria
- It is active against several mycobacteria only: active TB bacilli and M. avium complex.
- It is more effective against extracellular organisms
- Relatively less toxic and resistant strains develop slowly.

❖ Clinical use:

- Treatment of TB in combination with INH and rifampin to minimize resistance.
- Treatment of TB during pregnancy because it is the least toxic..

❖ Adverse effect

- Optic neuritis → ↓ visual activity, blurred vision and red-green color blindness.
- ↓ Urate excretion → may precipitate gout.

Anti- Tubercular drugs

5. Streptomycin: an aminoglycoside antibiotic, (Bactericidal).

- It is more effective against extracellular organisms
- **Therapeutic uses:** in combination with INH & rifampin to treat resistant pulmonary TB and renal TB (because 50-90% is excreted unchanged via the kidney).
- It is given by IM injections
- Infections due to streptomycin-resistant organisms may be treated with amikacin

❖ **Adverse effects**: nephrotoxicity and ototoxicity .

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥ 24

❖ Second Line Drugs :

1. Para Amino Salicylic acid (PAS).

- PAS is an analog of PABA; it works similar to sulfonamides but only against mycobacteria → **tuberculostatic** effect against extra and intracellular typical mycobacteria.
- Absorbed orally- metabolized by acetylation- metabolite is excreted in urine and is insoluble in acidic urine causing crystalluria.
- PAS is a reserve drug for the management of MDR-tuberculosis. It is replaced by ethambutol (resistance is common).

- **Adverse effect;** gastrointestinal irritation, peptic ulceration, hypersensitivity reactions, and effects on kidney, liver, and thyroid function.

2. Ethionamide:

- It is structurally similar to INH but is less efficacious.
- Given only orally and passes into BBB, Resistance develops rapidly
- **M.O.A:** similar INH blocks the synthesis of mycolic acids.
- It is **Tuberculostatic** on extra & intracellular mycobacteria but not necrotic tissue.
- Used in treatment of multidrug resistant TB.(in combination with quinolones)
- **Side effects**: peripheral neuropathy -optic neuritis-hepatotoxic, severe GI irritation hypothyroidism, hypoglycemia.

3. Polypeptides (viomycin , capreomycin ,inviomycin)

- Inhibition of bacterial protein synthesis. **Tuberculocidal** against extracellular organisms
- Capreomycin parenterally administered as second line drug used in the treatment of extensively and multi-resistant mycobacteria and atypical mycobacteria in HIV patients

- **Side effect:** Ototoxic and nephrotoxic

4. **Cycloserine**:

- It is an orally effective, **tuberculostatic** on extra & intracellular mycobacteria drug that inhibits cell wall synthesis.
- **Toxicity**: CNS manifeststions as headache, drowsiness, vertigo, seizures, and toxic psychosis.

5. **Fluoroquinolones:**

- The ciprofloxacin, levofloxacin, and moxifloxacin, are **Tuberculocidal** against extracellular organisms in the treatment of multidrug-resistant tuberculosis to first-line agents.
- Treatment of resistant TB organisms in combination with other antiTB drug, rifampicin , ethambutol , capreomycin.
- Prophylactic against TB in contact persons in combination with pyrazinamide

6. Bedaquiline:

- Specific inhibition on ATP synthesis in mycobacteria and is the first in a new class of drugs approved for the treatment of MDR-TB **(**pulmonary tuberculosis resistant to both isoniazid and rifampin)
- Tubeculocidal on extra & intracellualr mycobacteria
- Taken orally with food in order to maximize absorption

- **Adverse effects:** nausea, arthralgia, headache, cardiotoxicity, and hepatotoxicity.

❖ Regimens of treatment of T.B.:

- **Patients with active TB**:

– **Initial phase** (first 2 months): Rifampin + INH + Pyrazinamide + Ethmabutol).

- **Continuation phase** (next 4 months): at least 2 drugs are used (INH + rifampin).

- **Patients with latent TB** (i.e. patients with +ve Tuberculin skin test and had history of contact to a person proved to have TB):

- INH alone for 6 months or dual Rifampicin + INH for 3 months.

Anti- Tubercular drugs

- **Patients with meningeal TB**: As standard treatment but continuous phase is extended to 6 months + add corticosteroids.

- **TB during pregnancy**:

- the only anti-TB drug which is absolutely contraindicated is streptomycin. The other first line anti-TB drugs are safe for use in pregnancy.

- **TB with liver disease**: INH, rifampin, and pyrazinamide are hepatotoxic but because of their effectiveness, they should be used depending on monitoring of liver function tests. In severe liver damage, only one drug can be used.

- **INH resistant cases**

-Rifampicin +Pyrazinamide +Ethambutol + levofloxacin (LFX) (750 mg twice daily orally) for 6 months.

- **Multi drug resistant cases:** Refampicin or refampicin + INH resistant

- **Intensive phase** 4 drugs for 6 months: Pyrazinamide +Fluoroquinolone +Bedaquiline + linezolid

- **Continuation phase** 12-20 months: Stop pyrazinamide or bedaquiline

Anti- Lepral drugs

❖ Drugs used in leprosy:

- The standard therapy requires triple-drug regimen of (dapson, clofazimine and rifampicin) for 6 to 24 months

1. Dapson: structurally related to the sulfonamides

- **M.O.A**: inhibits dihydropteroate synthetase in the folate synthesis (**bacteriostatic**).

- **Therapeutic uses**: treatment of leprosy with rifampin + Clofazimine .
- also is used in the treatment of pneumonia caused by Pneumocystis in AIDS patients.

- **Adverse effects**: hemolysis (G-6-P D deficiency), methemoglobinemia, and peripheral neuropathy.

2. Clofazimine

- **M.O.A:** inhibit mycobacteria DNA synthesis (**bactericidal)**.
- Active against mycobacteria TB and leprosy
- **Therapeutic uses**: in combination with dapson and rifampin to prevent resistance.
- **Adverse effects**: abdominal pain, brown urine, atropine-like actions.

❑ **Treatment Regimen**: Drug Combination Orally for at least 2 years.
Dapson 100 mg/day+ Clofazimine 100 mg/day+ Rifampicin 600 mg/month.

Dr.Ng. Arkiawan

Antifungal drugs

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Fungal infection

- **Mycoses**: is infectious diseases caused by fungi.

- **↑ Fungal infections in patient with**:
  - ➢ Diabetes mellitus, cancer, AIDS, pregnancy and immunosuppressive therapy such as prolonged course of corticosteroids, broad-spectrum antibiotics, anticancer drugs

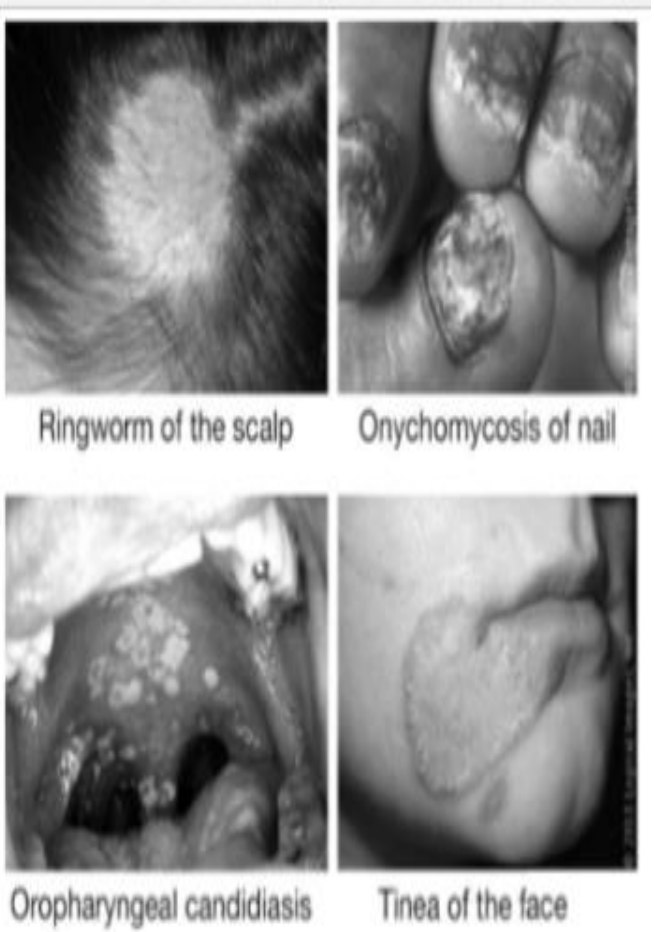
- **Types of fungal infection:**

❑ **Superficial mycosis:**.

- **Dermatophytes** (epidermis, skin, hair, nails) as : Tinea: Capitis (scalp), Corporis (body) & Pedis (foot)

- **Candida:** Cutaneous, vaginal, oropharyngeal and gastrointestinal candidiasis.

❑ **Systemic mycosis**. (lung) as candidiasis, cryptococcosis, aspergillosis → Fungal pneumonia ,gastroenteritis, endocarditis or meningitis.



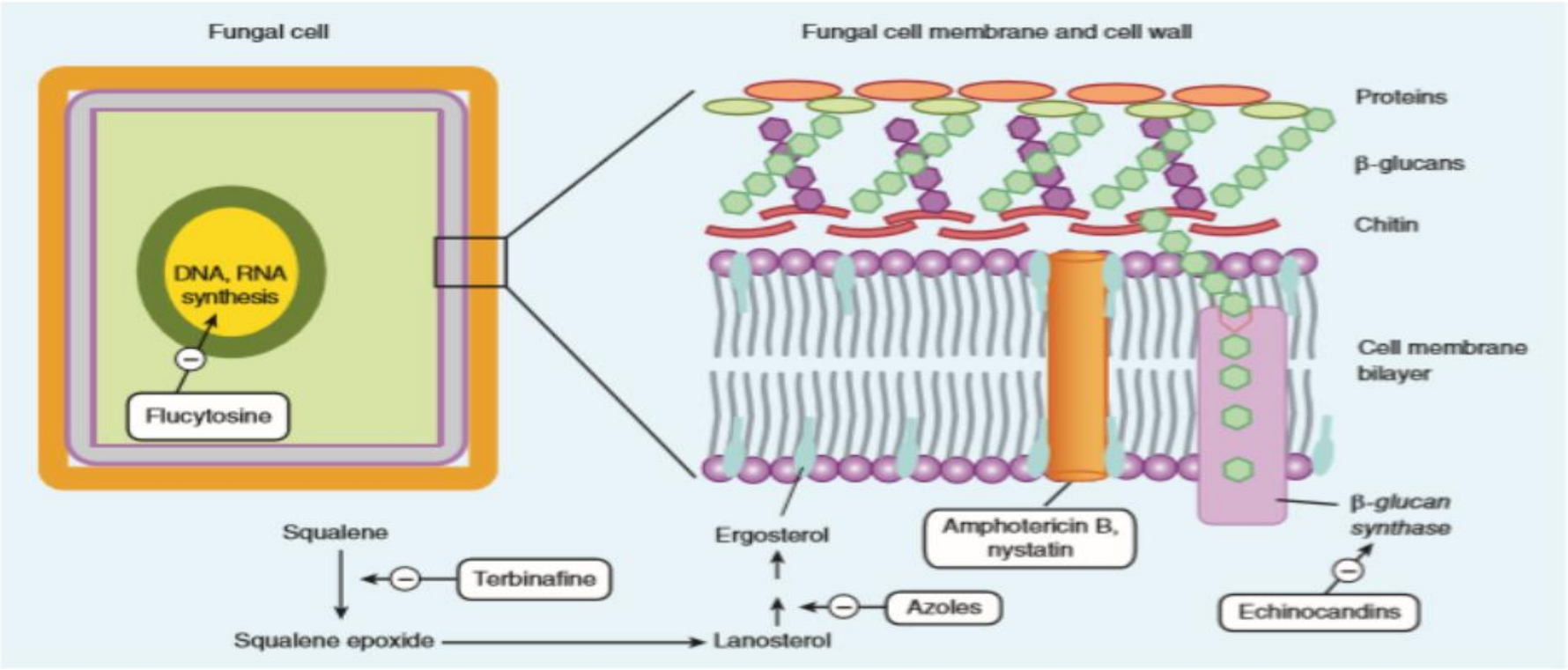
Fungal infection

- Fungi are eukaryotic, has:

  - Rigid cell walls composed of **chitin** (β-glucan synthase enzyme) rather than peptidoglycan in bacteria → treated by echinocandins drugs)

  - The cell membrane contains **ergosterol** rather than the cholesterol found in mammalian membranes (treated by azoles, polyenes and terbinafine).

  - The **nucleic acid synthesis** (treated by flucytosine) **and mitosis** (grisofulvin),



Fungal infection

- **Classification of the antifungal drugs**

- **Systemic drugs (oral or parenteral) for systemic infections**:
  - Amphotericin B
  - Flucytosine
  - Azoles: Ketoconazole, Fluconazole, itraconazole, voriconazole.
  - echinocandins: Caspofungin, micafungin

- **Drugs given systemically (Oral) for superficial infections**:
  - Azoles: ketoconazole, fluconazole, itraconazole: used for dermatophytes-candida.
  - Griseofulvin, Terbinafine: used for Dermatophytes

- **Topical drugs for superficial infections:**
  - Azoles: ketoconazole-miconazole-clotrimazole: (dermatophytes-candida).
  - Nystatin: (Candida).
  - Terbinafine: (dermatophytes).

NB:

- **Antifungal antibiotics**: Amphotericin B, nystatin (polyene antibiotic), and griseofulvin.
- Superficial fungal infections are treated first with topical agents

Antifungal drugs

A) Systemic drugs for systemic infections:

1. Amphotericin B (Polyene, antifungal antibiotic related to nystatin):

❖ Pharmacokinetics:

- Not absorbed orally (polar), given orally only in GIT infection.
- Given by I.V. infusion, intra-thecal, and topical on eye, nose.
- Protein Bound, widely distributed to all tissues except the BBB.
- Excreted slowly in the urine over a period of several days. half-life 15 days.

❖ M.O.A.: **fungicidal action**

➢ Binds to ergosterol in the fungal cell membrane → formation of channels → leakage of fungal cell content as electrolytes → death of fungal cells.

❖ Antifungal spectrum: widest spectrum

➢ **All fungi that cause systemic infection**: Candida, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides, Blastomycoses and Aspergillus

- **Against protozoal infection** as, leishmaniasis.

❖ **Therapeutic uses:**. Highly efficacious but highly toxic (azoles, fluconazole and itraconazole replaced it).

1. DOC for several life-threatening mycoses such as:.

- Sever fungal pneumonia, cryptococcal meningitis and disseminated infections with histoplasmosis or coccidioidomycosis

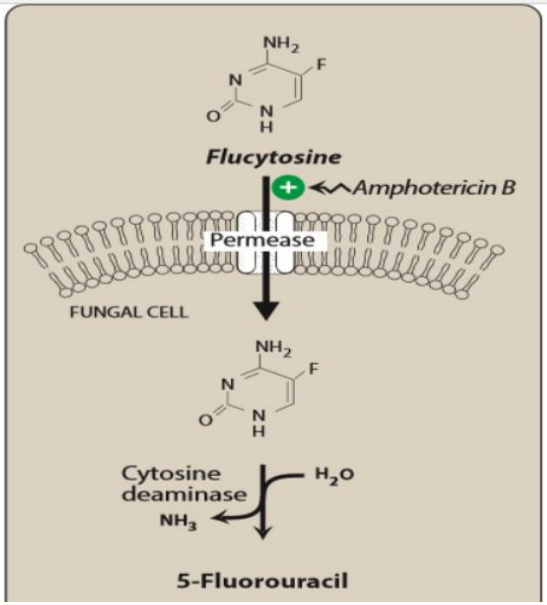
2. Treatment of mycotic corneal ulcers and keratitis
3. Treatment of the protozoal infection leishmaniasis

- **Dose**: Slow IV infusion, 0.5–1 mg/kg/d
  Liposomal Amphotericin B: 3-6 mg/kg/d IV → ↓ renal and infusion toxicity

❖ **Adverse effects**

- **Infusion related (I.V infusion)**: Fever, chills. muscle spasms, vomiting
- **Hypokalemia and nephrotoxicity**.
  - Azotemia is exacerbated by other nephrotoxic drugs, as aminoglycosides, cyclosporine, , and vancomycin,
- **Aplastic anemia** & Thrombophlebitis.

2. Flucytosine (Antimetabolite):



❖ **P. k.:** Absorbed orally- passes BBB-excreted in urine, must be adjusted in patients with renal dysfunction.

❖ **M.O.A: Fungistatic action**

- Converted into 5-Fluorouracil (by cytosine deaminase) → inhibit DNA & RNA (nucleic acid synthesis). .

❖ **Antifungal spectrum:** Narrow spectrum .

- Act against some strain of candida, cryptococcus and Chromoblastomycosis .

❖ **Therapeutic uses: (**only oral, not used alone, to avoid the development resistance)

- **Used in combination with:**
  - Amphotericin B for treating candidiasis and cryptococcosis meningitis.
  - Itraconazole → Synergism for treating chromoblastomycosis.

❖ **Adverse effects**

- **Bone marrow depression**: anemia, thrombocytopenia and neutropenia
- Hepatotoxic
- Gut upsets and entero-colitis.

Antifungal drugs

3. Azole antifungals: Safer, wide spectrum

- **Classification to :**

1. The **imidazoles**
   - ketoconazole, → topical, oral for cutaneous and systemic fungal infections.
   - Miconazole, clotrimazole → only topical for cutaneous infections.

2. The **triazoles**:
   - Itraconazole, fluconazole, voriconazole, and posaconazole → given systemically (oral, parenteral) for the treatment or prophylaxis of the cutaneous and systemic fungal infections

- Triazoles are less toxic than imidazole.

❖ **Mechanism of action: Fungistatic**

- Inhibition of ergosterol synthesis of cell membrane by inhibiting CYP450 dependent14-a demethylase that converts lanosterol to ergosterol.→ disrupt cell membrane function → inhibit cell growth.

❖ **Spectrum of activity:** Broad spectrum

- Candida, Cryptococcus neoformans.
- Dermatophytes (endemic) mycoses, blastomycosis, coccidioidomycosis, histoplasmosis.
- Itraconazole and voriconazole, are effect against Aspergillus infections.

Antifungal drugs

1. Ketoconazole (Nizoral): Shampoo, Orally for systemic & cutaneous

❖ Pharmacokinetics:

- Absorbed orally, Stomach HCI → ↑ absorption. & - food → ↓ absorption.
- Cannot pass BBB. Extensively metabolized by the liver, metabolites are excreted in bile.
- Stronger inhibit CYP 450

N.B.:

- ketoconazole inhibits synthesis of testosterone and Corticosteroids. → Gynecomastia, loss of libido and azoospermia in males.
- Avoid combination with: Antacids or H2 blockers & Amphotericin B

❖ Therapeutic uses:

1. **Dermatophytosis:** topically for hair dandruff (Nizoral shampoo).
2. **Systemic fungal infections** but not in fungal meningitis: orally, oesophageal and vulvovaginal candidiasis (very toxic for systemic use; hence it has been replaced by triazoles

❖ Adverse effects:

- Hepatotoxicity. - Allergy. Gut upsets
- Gynecomastia, impotence, loss of libido, and infertility. .
- HME inhibitor → inhibits the metabolism of sulfonylureas, warfarin, phenytoin, terfenadine

2. Fluconazole: Oral or IV

- Better absorbed orally and not affected by food or antacids drugs
- Passes BBB, to body fluids and tissues.
- Not HME inhibitor.
- Highly active against Cryptococcus neoformans, coccidioidomycosis and certain species of Candida

❖ **Advantages of fluconazole and itraconazole over ketoconazole**

- Less toxic (less effect on human cyt P450): less hepatotoxic
- no inhibition of testosterone synthesis, no gynecomastia or infertility
- less drug interactions.
- More effective.

.

❑ **Uses** of Fluconazole **:**

- **Cryptococcal meningitis**: **DOC**
- **Candidiasis:** treatment of candidemia (echinocandins more activate).
- **Mucocutaneous candidiasis** (esophageal, oropharyngeal and vaginal candidiasis).
- **coccidioidomycosis meningitis**.
- **Prophylactic use:** reduce fungal disease in bone marrow transplant and AIDS patients

3. Itraconazole: Oral, I.V;

- Has a broad antifungal spectrum compared to fluconazole.
- Food and low gastric pH. → ↑drug absorption (oral capsule) .
- Distributes well in most tissues, poorly pass into the BBB.
- Metabolized by the liver, excreted in the feces and urine.
- HME inhibitor

❖ Uses:

- 1st **choice in** systemic infections: blastomycosis, sporotrichosis, and histoplasmosis.
- **In esophageal candidiasis:** active against some strains resistant to fluconazole.
- Treatment of dermatophytosis and onychomycosis.
- Treatment of Candida and Aspergillus (Voriconazole or Posaconazole more effective).

❖ Adverse effects:

- Nausea, vomiting, rash, hypokalemia, hypertension, edema, and headache.
- Hepatotoxicity.
- should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

4. Voriconazole (orally, IV.)

- It is similar to itraconazole in its spectrum of action, having excellent activity against **Candida** sp (including fluconazole-resistant species), **aspergillosis.**.

- **DOC** for invasive aspergillosis as replaced of amphotericin B (less toxic than amphotericin B.
- Treatment of candidiasis infection (fluconazole-resistant organisms). candida esophagitis and stomatitis.

- **Adverse effects:**. Skin rash and elevated hepatic enzymes. Visual disturbance.

5. Posaconazole (orally , IV.)

- The broadest-spectrum triazole, has activity against most species of **Candida** and **Aspergillus and mucormycotisis (**Rhizopus)
- Absorption is improved with meals high in fat and gastric HCL.
- **used** for prophylaxis of fungal infections during cancer chemotherapy and in salvage therapy in invasive aspergillosis.

❖ **Contraindications**:

- **Azoles:** teratogenic, and they should be avoided in pregnancy

Antifungal drugs

4. Echinocandins: only i.v. formulation

- Caspofungin, micafungin, and anidulafungin
- Active against **Aspergillus** and **Candida** (including those species resistant to **azoles**) but not **Cryptococcus neoformans.**

- The drugs distribute widely to the tissues and are eliminated largely via hepatic metabolism.
- Caspofungin has a half-life of 9–12 h. The half-life of micafungin is slightly longer, and that of anidulafungin is 24–48 h.

❖ Mechanism of action: Fungicidal

- Inhibits the synthesis of β-glucan synthase enzyme → inhibit cell wall synthesis → lysis and cell death.

❖ Clinical Uses

- Caspofungin: in Candidiasis, candidemia, (**First-line**) & invasive aspergillosis refractory to amphotericin or an azole. (**Second-line**).

- Micafungin and anidulafungin: treatment of invasive candidiasis candidemia

- Micafungin is also indicated prophylaxis of invasive Candida infections in patients who are undergoing hematopoietic stem cell transplantation.

❖ Adverse effects

- fever, rash, nausea, and phlebitis at the infusion site.
- They can also cause a histamine-like reaction (flushing) when infused too rapidly.
- Caspofungin should not be coadministered with cyclosporine → ↑ hepatic transaminases.

NB: Anidulafungin can be administered in severe hepatic dysfunctin, not substrates for CYP450 enzymes and do not have any associated drug interactions.

Antifungal drugs

B) Oral systemic drugs for superficial fungal infections: dermatophytes or tinea

- griseofulvin, terbinafine, and several azole (fluconazole, itraconazole).

1. Griseofulvin (oral only, not effect topically)

- Absorbed orally - Concentrated in keratinized tissues: hair and nails- Extensively metabolized by the liver. Induces hepatic CYP450 activity, →drug interaction.

❖ **Mechanism of action**: **fungistatic**

- Concentrated in newly formed keratin preventing its infection by:

- Binding with microtubules of the mitotic spindle → ↓ fungal mitotic division & Inhibiting nucleic acid synthesis.

❖ **Therapeutic uses:**

- Treatment of dermatophytes infections (skin and nail). replaced by terbinafine and the azoles.
- long term therapy, i.e. 2–6 weeks for skin and hair infections, 6- 12 months for nail infection (onychomycosis).

❖ **Adverse effects**

- GIT disturbances. - Allergic reactions. - Teratogenic.
- H.M.E inducer. drug interactions with warfarin and phenobarbital.

2. Terbinafine: synthetic allylamine , Oral & topical

- Like griseofulvin, terbinafine is a keratophilic medication.
- More effective than either itraconazole or griseofulvin with a shorter duration of therapy.

❖ **Mechanism of action**:

- It interferes with ergosterol biosynthesis.
- Inhibits fungal enzyme squalene epoxidase → accumulation of the sterol squalene (toxic to the organism) → Inhibit ergosterol synthesis → cell death

❖ **Therapeutic uses**

- Dermatophyte, onychomycoses (fungal infections of nails): **1st choice**, 250 mg orally/d for 12 weeks

❖ **Adverse effects**:

- nausea, diarrhoea, dyspepsia and rarely hepatitis. It may cause
- itching, rashes, local irritation on topical use.

C) Topical antifungals:

1-Nystatin:

❖ **Pharmacokinetics:**

- Not given systemically because of its toxicity nephrotoxicity.
- It is given orally (not absorbed) and locally on skin and vagina.

❖ **Mechanism of action**: as amphotericin. (**Fungicidal action**)

❖ **Therapeutic uses:** for oropharyngeal and intestinal candidiasis, intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.

❖ **Adverse effects** are rare after oral administration, but nausea and vomiting. Topical and vaginal forms may cause skin irritation.

2- **Topical azole**:

Example: Miconazole –Econazole, Clotrimazole, ketoconazole.

- The two azoles most used topically are clotrimazole and miconazole
- Given as cream, ointment and vaginal suppositories.
- useful for dermatophytic infection: body (tinea corporis), groin (tinea cruris), foot (tinea pedis), vulvovaginal candidiasis
- Absorption is negligible, and adverse effects are contact dermatitis, vulvar irritation, and edema (rare).

3- Topical allylamines

- Terbinafine and naftifine are allylamines available as topical creams.
- Both are effective for treatment of tinea cruris and tinea corporis.

Antifungal Agents and their Uses

Drugs	Activity and uses
Amphotericin B	Aspergillosis, Blastomycosis, Candidiasis, Cryptococcosis Coccidioidomycosis, Histoplasmosis, Mucormycosis, Sporotrichosis
Flucytosine	Cryptococcosis, Candidiasis (some species) Chromoblastomycosis
Ketoconazole	Candidiasis, Dermatophytosis
Fluconazole	Cryptococcosis, Candidiasis, Coccidioidomycosis
Itraconazole	Candidiasis, Dermatophytosis, Blastomycosis, Histoplasmosis, Coccidioidomycosis, Aspergillosis Sporotrichosis
Voriconazole	Aspergillosis, Candidiasis
Posaconazole	Candida, Aspergillus, mucormycosis.
Caspofungin	Candidiasis, Aspergillosis
Griseofulvin (Oral)	Dermatophytosis only
Terbinafine	Dermatophytosis, Candidiasis
Nystatin	Candidiasis only

- **Treatment of specific fungal infection**

1. Aspergillus

- Species can cause an invasive fungal infection that affects the lung.
- In immunocompromised individuals it can invade more widely and infect the heart, brain, sinuses and skin.

- **Treatment**: voriconazole (1st choice), more effective and less toxic than amphotericin.
- Itraconazole (2nd choice).
- Caspofungin, or another echinocandin, is reserved for infections that have failed to respond to standard treatments.

2. Candida

- **Treatment:**

- Nystatin is often used for oral candidiasis (oropharyngeal disease)
- If there is oropharyngeal disease that is refractory to topical treatment, an absorbed drug such as fluconazole or itraconazole is used orally.

- Vulvovaginal infection is treated with cream and pessaries; clotrimazole (1st choice). Nystatin (2nd choice).

Antifungal drugs

- Superficial candidal infections of the skin are treated topically with cream, usually containing an imidazole. Terbinafine or nystatin can also be used topically.

- Invasive candidiasis as a hospital-acquired infection, particularly in people who have had abdominal surgery, parenteral nutrition, multiple antibacterial drugs are treated by Amphotericin or caspofungin (1st choice). Fluconazole, itraconazole, voriconazole are alternative.

3. Cryptococcus

- It can cause life-threatening meningitis.
- **Treatment:** amphotericin **or** fluconazole (1st choice),
- Amphotericin +/- flucytosine is an alternative

4. Skin and nail infections

- Topical therapy is usually suitable for infections with most dermatophytes.
- Fungal infection of the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum), foot (tinea pedis) or nail (tinea unguium) will respond to most azoles.

- Griseofulvin is treatment of scalp infections.

- Nail infection usually requires systemic treatment with terbinafine or itraconazole.

5. Prophylaxis in immunocompromised individuals

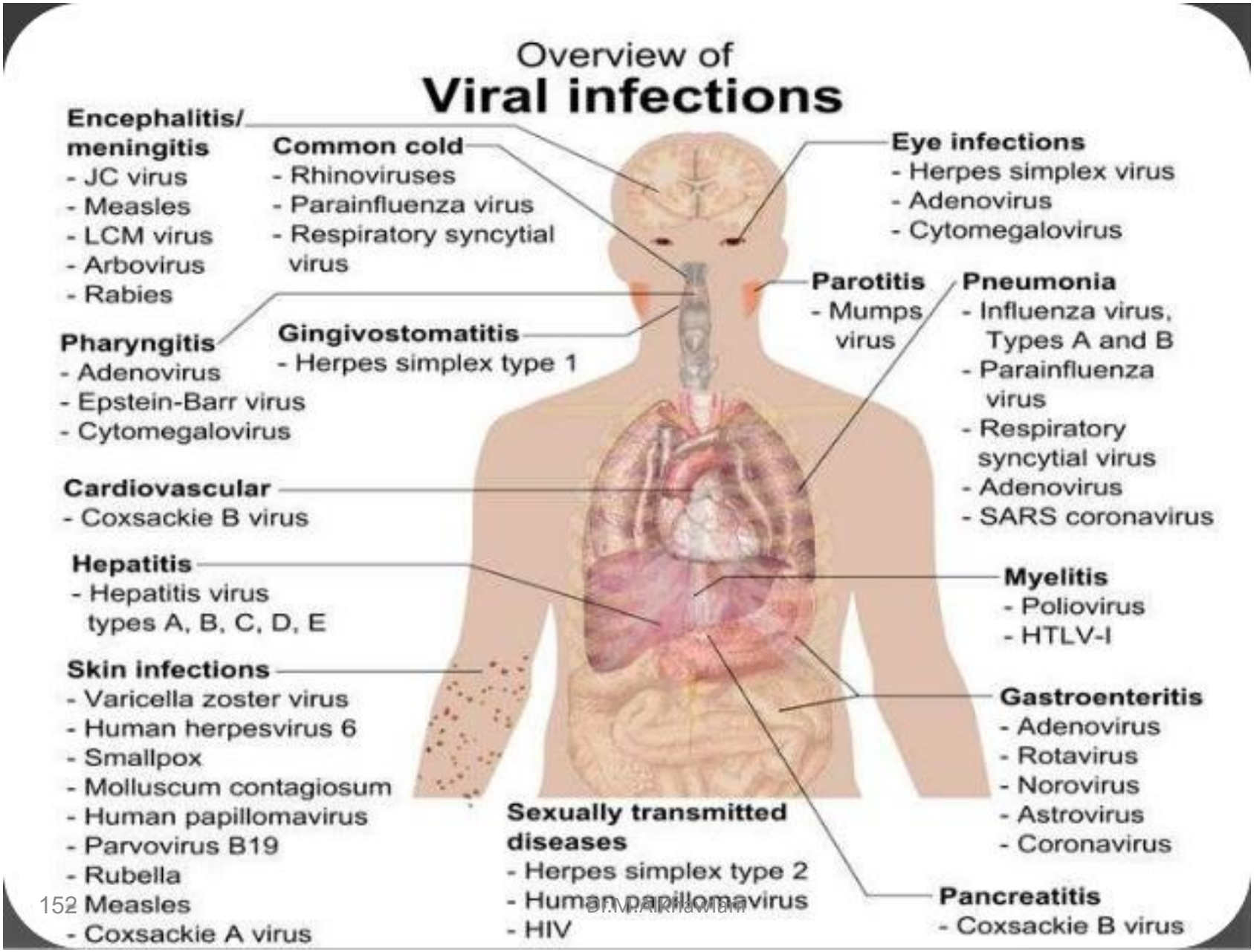
- Individuals who are immunocompromised are at greater risk of fungal infection.
- Prophylaxis is often given with oral fluconazole, since this has better oral absorption than most azoles.

Antiviral drugs

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Assist. Professor of pharmacology and Toxicology

Viral infection



Viral infection

- A virus is a small infectious agent that replicates only inside the living cells of other organisms.

❖ Types of viruses

- **DNA viruses**: e.g. herpesviruses, cytomegalovirus and hepatitis B virus.
- **RNA viruses**: influenza, hepatitis C, Respiratory syncytial virus
- **RNA retroviruses:** e.g. HIV (contain an enzyme, reverse transcriptase),

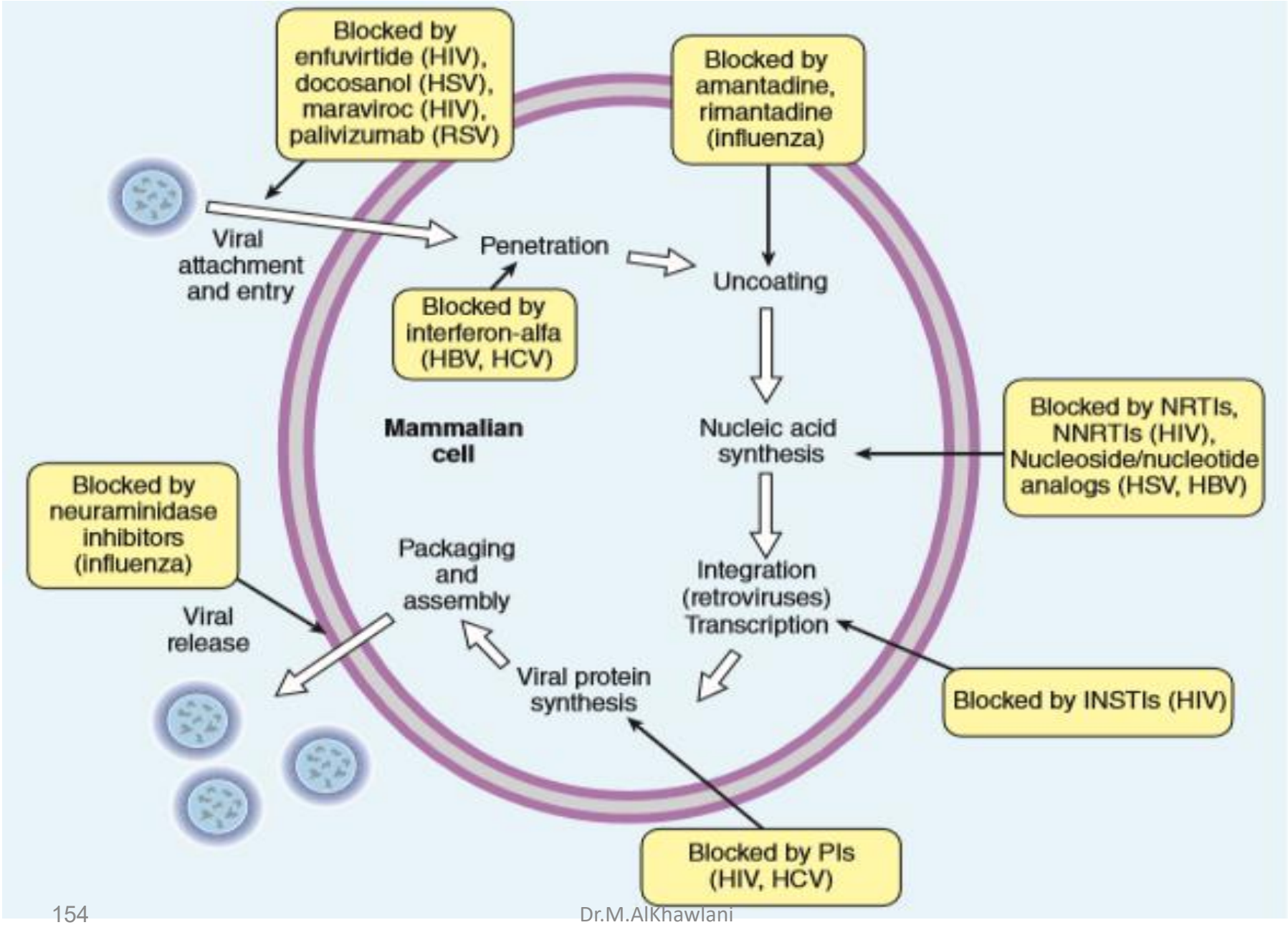
❖ Viral replication requires several steps:

(1) Attachment of the virus (2) **Entry** (3) **Uncoating** of viral nucleic acid

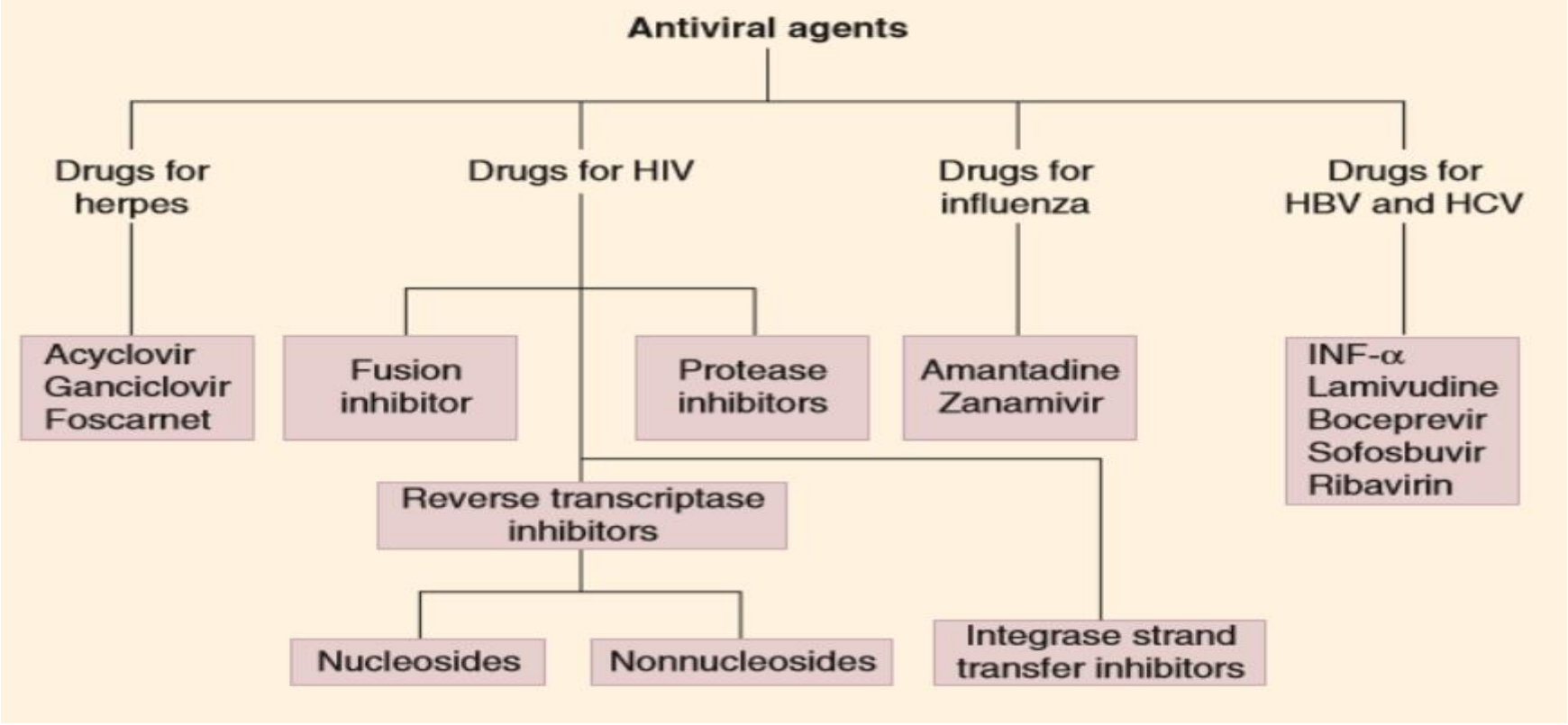
(4) **Synthesis** of new viral RNA or DNA (5**) Integration** into the nuclear genome

(6) **Assembly (maturation**) of viral particles (7**) Release** from the cell.

Viral infection


Blocked by enfuvirtide (HIV), docosanol (HSV), maraviroc (HIV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs, NNRTIs (HIV), Nucleoside/nucleotide analogs (HSV, HBV)
Blocked by neuraminidase inhibitors (influenza)
Packaging and assembly
Integration (retroviruses) Transcription
Viral release
Viral protein synthesis
Blocked by INSTIs (HIV)
Blocked by PIs (HIV, HCV)

Antiviral drugs

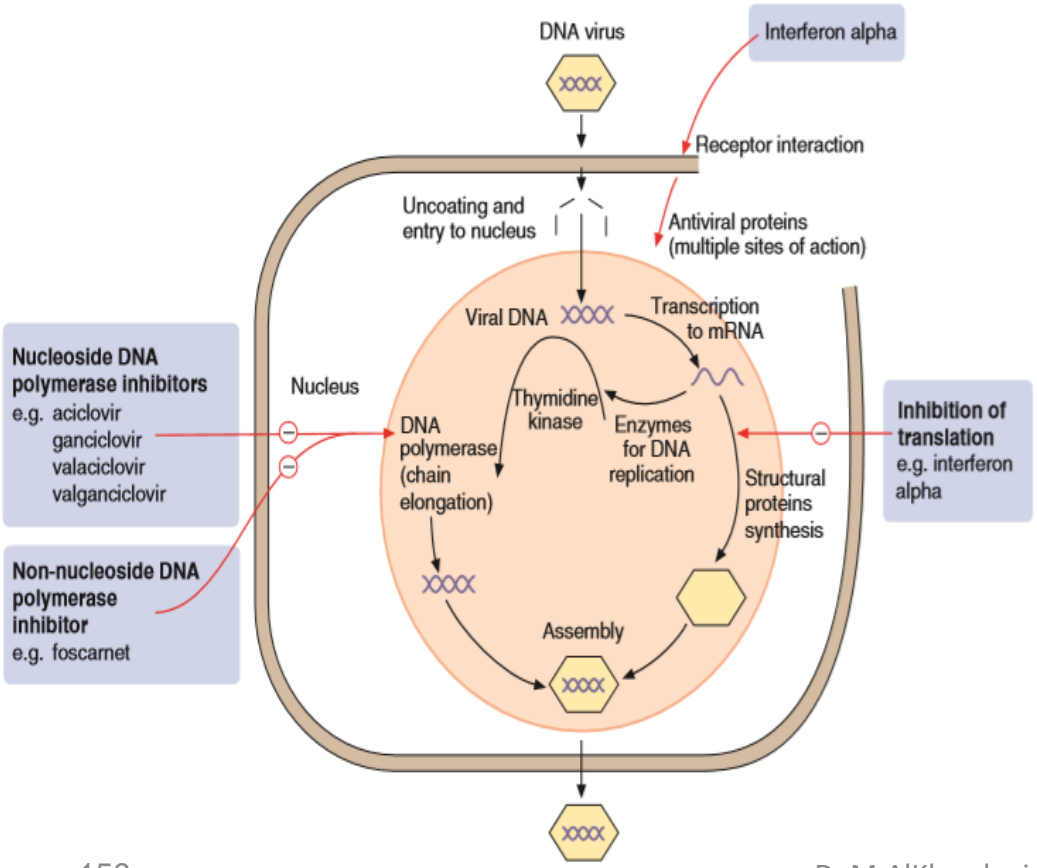


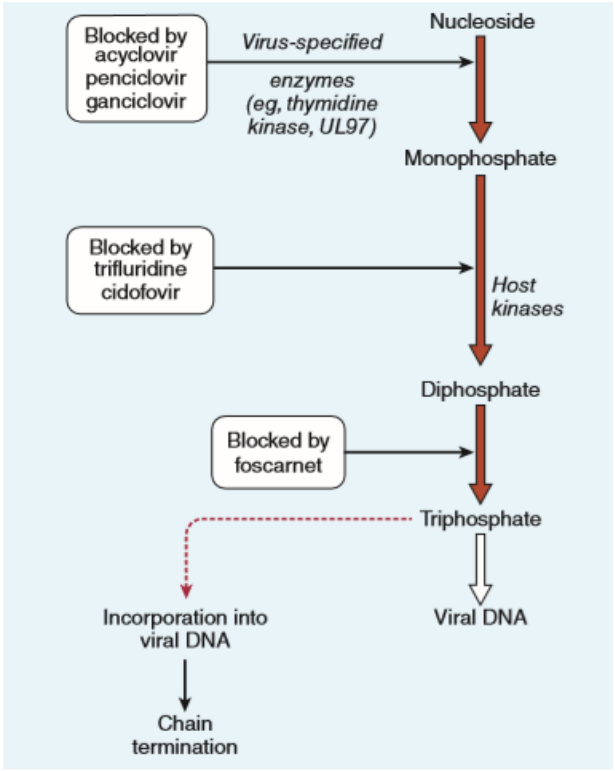
Antiviral drugs

1- Antiviral for herpes virus infections:

- Herpes virus is large family of DNA virus
- Drugs used for herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalo virus (CMV).

❖ Example: Acyclovir, valacyclovir, famciclovir, penciclovir, ganciclovir, foscarnet, Cidofovir.

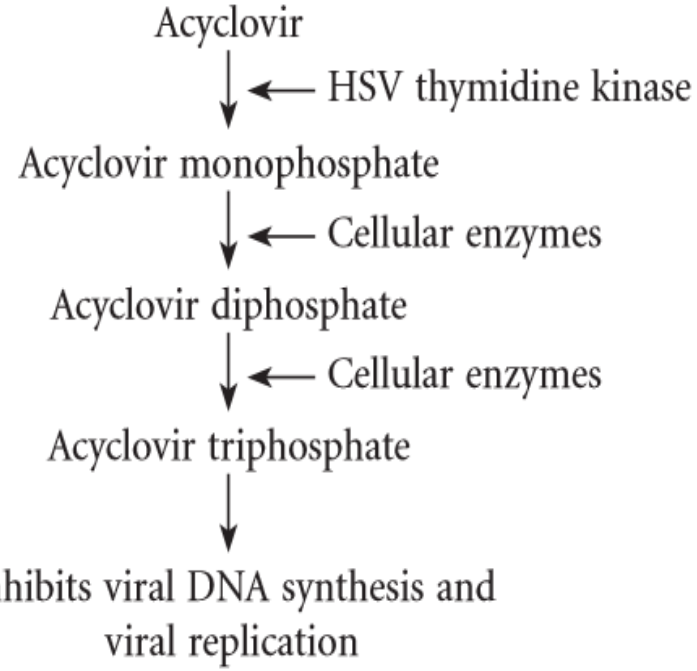




Antiviral drugs

1. Acyclovir

- Guanosine nucleoside analogue, more effective against HSV than VZV infections. Given orally, IV, and topical on eye and skin



❖ **M.O.A**: Inhibit viral DNA polymerase.

❖ **Resistance**: Altered or deficient thymidine kinase and DNA polymerases.

❖ **Uses:**

- **DOC in HSV of:**
  - **Mucocutaneous HSV**: herpes labialis and ulcers in mouth.
  - **Intravenous acyclovir:** encephalitis, neonatal HSV infection.
  - **Genital herpes lesions** and for prophylaxis in immuno-compromised patients (eg, AIDS).
- **Also in** VZV. (chickenpox and herpes zoster).
- **Adverse effects**: Local irritation. (topically), Headache, diarrhea, nausea and vomiting(orally) Transient renal dysfunction (renal Stones). (IV).,

Antiviral drugs

2. **Valacyclovir:** prodrug of acyclovir, greater oral bioavailability and longer duration of action

3. Penciclovir: only administered topically for treatment Herpes simplex labialis

4**. famciclovir:** orally. Prodrug penciclovir, greater oral bioavailability, used for acute herpes zoster, genital HSV infection, and recurrent herpes labialis.

5. Ganciclovir: oral, IV. greater activity against CMV, used for treatment and prophylaxis of severe CMV infection (retinitis, pneumonia, gastroenteritis). more toxic than acyclovir (**S.E**: myelosuppression (neutropenia), carcinogenesis and teratogenic action

6. Cidofovir: cytosine analogue, active diphosphate inhibits DNA polymerases of HSV, CMV, **Used:** in CMV retinitis, and acyclovir and ganciclovir-resistant (does not require viral kinase). Given by IV or intravitreal injection. Nephrotoxicity, neutropenia and metabolic acidosis are the main side effect.

7. Foscarnet: Given IV, inhibits DNA polymerase, RNA polymerase directly(does not require viral kinase or cellular kinases). **Uses:** in CMV retinitis and for acyclovir-resistant HSV and VZV infections. **Side effects**: Nephrotoxicity, anemia, , genital ulceration

2- Antiviral against respiratory virus infections:

- Viral respiratory tract infections:
  - Influenza A & B
  - Respiratory syncytial virus (RSV).

A. Neuraminidase inhibitors

Oseltamivir (Tamiflu)® **&** **Zanamivir**

- **M.O.A:** selectively inhibit neuraminidase, → preventing the release of new virions and their spread from cell to cell.
- Effective against both type A and B influenza and swine flu (H1N1) viruses.

- **Used:** the treatment and prophylaxis of influenza infection
- Administered within 24 - 48 hours after the onset of symptoms, decrease the intensity and duration of symptoms

- Oseltamivir: orally active prodrug, rapidly hydrolyzed by the liver to its active form.
- Zanamivir: not active orally and is administered via inhalation

- **Side effect** is GIT discomfort
- Zanamivir is contraindicated in asthmatic patients. (bronchospasm effect)

B. Adamantines derivatives .

Example: Amantadine & Rimantadine (Oral administration)

- **M.O.A:** Inhibit uncoating of the viral RNA → preventing its replication.
- Active only against influenza A (but not influenza B), (H1N1 strain is resistant to the adamantines)
- **used as** prophylactic against influenza A virus infection and can reduce the duration of symptoms if given within 48 h after contact.
- Amantadine also has anti-parkinsonian effect.
- Rimantadine is more potent than Amantadine
- Substituted by neuraminidase inhibitors (due to CNS toxicity & resistance)

❖ **Adverse effects**: Nausea, anorexia and CNS: insomnia, dizziness, psychosis (Amantadine

C. Ribavirin: inhalation, orally and i.v. .

- Broad spectrum antiviral active against DNA and RNA virus including:
  - Respiratory syncytial virus (RSV), influenza A and B,
  - Hepatitis C (in combination with interferon-α)

❖ **M.O.A.**:

- It block RNA-dependent RNA polymerases in RNA virus → inhibit viral replication.
- It inhibits DNA virus by inhibition of guanosine synthesis → inhibit viral replication.

❖ **Therapeutic uses**:

- Severe RSV bronchiolitis or pneumonia (inhalation).
- Also use to influenza A and B infections.
- Chronic hepatitis c infection (HCV) in combination with interferon α.

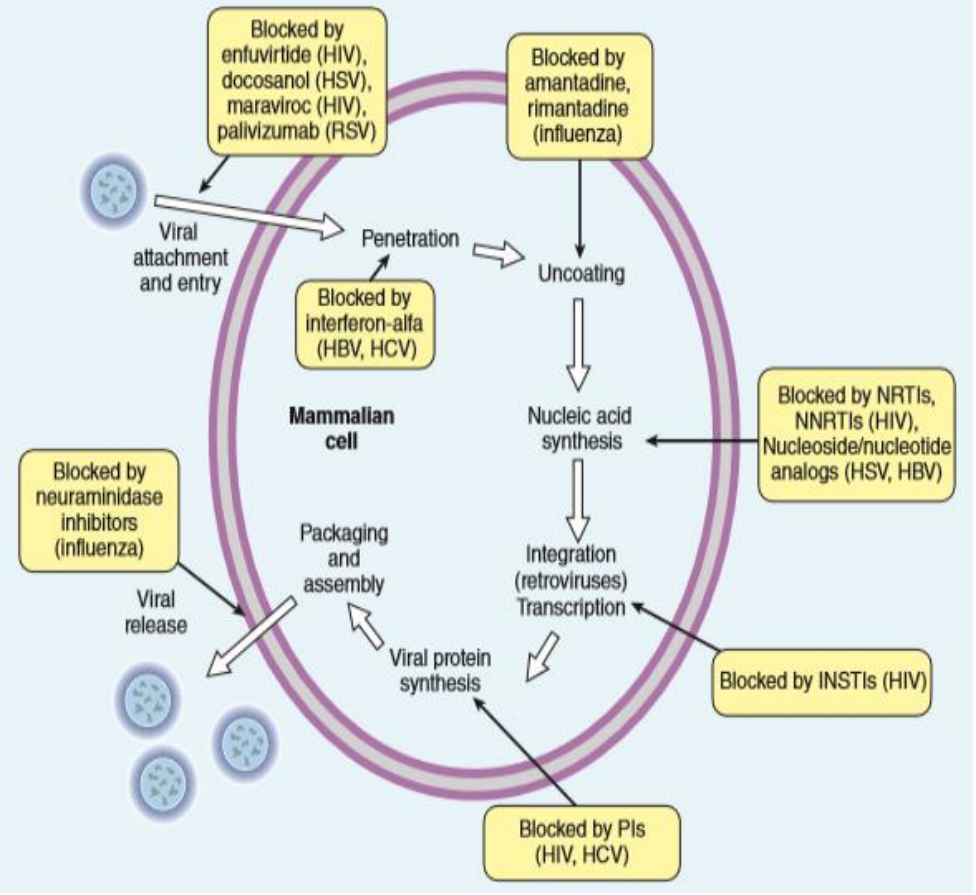
❖ **Adverse effects:** Hemolytic anemia and teratogenic in pregnancy.

3- Antiviral against hepatic viral infections:

- Hepatitis B (HBV) (DNA virus) and hepatitis C (HCV) (RNA virus) are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma.

- seven drugs were approved for treatment of chronic HBV infection:
  - Two injectable: interferon-α (IFN-α), and peginterferon-α
  - oral nucleoside/nucleotide analogs: lamivudine, adefovir, entecavir, telbivudine, tenofovir.

- For chronic hepatitis C virus (HCV), protease inhibitor (such as boceprevir or telaprevir) should be added to pegylated interferon and ribavirin.


Blocked by enfuvirtide (HIV), docosanol (HSV), maraviroc (HIV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs, NNRTIs (HIV), Nucleoside/nucleotide analogs (HSV, HBV)
Blocked by neuraminidase inhibitors (influenza)
Packaging and assembly
Integration (retroviruses) Transcription
Viral release
Viral protein synthesis
Blocked by INSTIs (HIV)
Blocked by PIs (HIV, HCV)

❖ For chronic hepatitis B virus (HBV)

1. Interferon alpha (IFNs-α) and peginterferon-α

- They are glycoproteins secreted from the host cells in response to viral infection
- IFNs-α given IV, IM or SC. three times weekly (not absorbed orally).
- Elimination of IFN-α is mainly via proteolytic hydrolysis in the kidney.

- peginterferon-α :The polyethylene glycol-conjugated (pegylated) form has more persistence levels in the blood and is given SC once weekly.

❖ M.O.A:

- ➢ They induce the production of enzymes in host cell ribosomes → inhibit viral mRNA translation to viral proteins → inhibit viral replication
- ➢ Inhibition of viral penetration.
- ➢ Stimulation of host immunity

❖ Clinical uses:

1. **Short acting interferon α** is used by SC or IM for treatment of:
   - HBV: 5-10 million units 3 times /week for 4-6 months,
   - HCV: 3 million units 3 times/week for 6 months, in combination with ribavirin
   -also used in Some malignant diseases as leukemia, myeloma and Kaposi sarcoma

2. Long acting peginterferon α:is used by SC for:

- HBV: 180µg(one ampoule / week)
- HCV: with ribavirin (more effective than the combination IFNs-α and ribavirin)

❖ **Side effect:**

- Nephrotoxicity and thyroiditis: Due to stimulation of immune system (autoimmune)
- flu like symptoms (fever ,chills , muscle pain) , bone marrow suppression (neutropenia). Due to inhibition of DNA of host cells:

2. Lamivudine, Entecavir, Tenofovir, Adefovir and Telbivudine

- It is a nucleoside reverse transcriptase inhibitor (NRTI) → blocking the HBV polymerase and HIV reverse transcriptase.

- **Lamivudine:** a cytosine analog that inhibits both HBV DNA polymerase - HIV reverse transcriptase. **Used:** HBV (100 mg/ once day) & in combination with other drugs against HIV. **S.E:** remarkably nontoxic (headache and dizziness).

- **Adefovir:** inhibits HBV DNA polymerase → **Used** in treatment of HBV (10 mg orally once a day) and in lamivudine resistant strains of HBV. **S.E:** Nephrotoxicity and severe hepatomegaly.

Antiviral drugs

- **Entecavir:** a guanosine analog → inhibits HBV DNA polymerase and HIV reverse transcriptase. → **Used** in lamivudine resistant strains of HBV (orally once a day, (affect by food).

- **Telbivudine:** a thymidine analog → inhibits HBV DNA polymerase → **Used** in lamivudine resistant strains of HBV (orally once a day).

- **Tenofovir** (category B), inhibits HIV reverse transcriptase (antiretroviral drug, used for HIV), is also approved for chronic HBV infection and is active against lamivudine- and entecavir resistant strains.

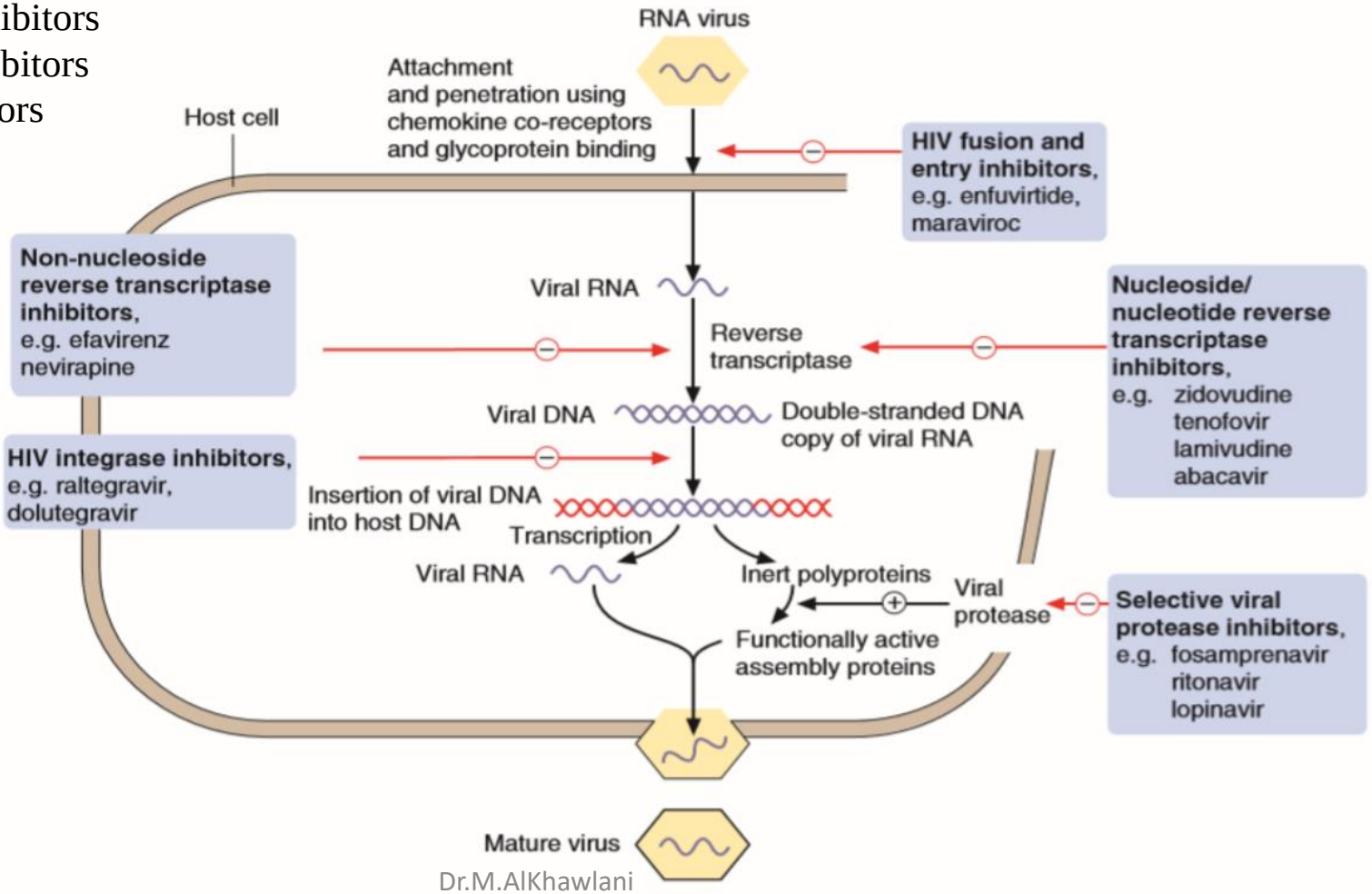
❖ For chronic hepatitis C virus (HCV)

- **Boceprevir and telaprevir (For HCV)**
  - Inhibit HCV replication directly act as protease inhibitor.
  - Used in combination with peginterferon alfa + ribavirin → improve response rates and reduce the emergence of viral resistance.
  - Because both drugs are strong inhibitors of CYP3A4/5, → drug interactions.

  - **Adverse effect:** rash, anemia.

4- Antiviral against HIV infections (AIDS) - Antiretroviral drugs

- Human immunodeficiency virus (HIV) belongs to the RNA-retroviruses.
- There are five classes of antiretroviral drugs:
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Integrase inhibitors
- Protease inhibitors
- Entry inhibitors


RNA virus
Attachment and penetration using chemokine co-receptors and glycoprotein binding
Host cell
HIV fusion and entry inhibitors, e.g. enfuvirtide, maraviroc
Non-nucleoside reverse transcriptase inhibitors, e.g. efavirenz nevirapine
Viral RNA
Reverse transcriptase
Nucleoside/ nucleotide reverse transcriptase inhibitors, e.g. zidovudine tenofovir lamivudine abacavir
Viral DNA
Double-stranded DNA copy of viral RNA
HIV integrase inhibitors, e.g. raltegravir, dolutegravir
Insertion of viral DNA into host DNA
Transcription
Viral RNA
Inert polyproteins
Viral protease
Selective viral protease inhibitors, e.g. fosamprenavir ritonavir lopinavir
Functionally active assembly proteins
Mature virus

Life cycle of HIV and the classes of antiretroviral drugs

Antiviral drugs

Antiretroviral drugs

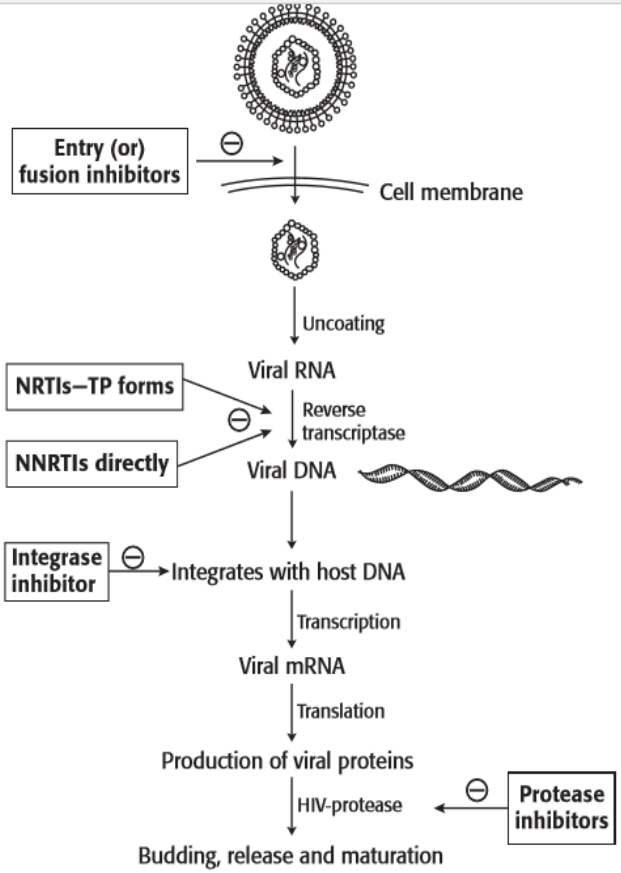
A. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

❖ **Preparation:**

- Zidovudine, Didanosine , Stavudine – Abacavir, Lamivudine and Emtricitabine.

❖ **Mechanism of action of NRTIS:**

- phosphorylated by cellular enzymes to the triphosphate form → Competitive inhibition of viral reverse transcriptase (viral RNA dependent DNA polymerase) → viral DNA chain termination.



- Human DNA polymerase is relatively resistant to the effect of these drugs.
- However, mitochondrial DNA polymerase in human cell is more susceptible, → some unwanted effects.

- All drugs completely absorbed from the gut.
- All drugs primarily renally excreted, and all require dosage adjustment in renal insufficiency except abacavir, which is metabolized by alcohol dehydrogenase and glucuronyl transferase.

Antiviral drugs

1. Zidovudine (AZT) or azidothymidine: a thymidine analog, was the first agent available for the treatment of HIV infection, crosses placenta and BBB, metabolized in liver by glucuronide conjugation

- Zidovudine is used in treatment of HIV(ATDs) in:
  - children and adults (300 mg orally /12 h)
  - To prevent transmission of HIV virus from mother to fetus (first-line agents for use in pregnant women).
  - for prophylaxis in individuals exposed to HIV infection ..

NB: Zidovudine is available in a fixed-dose formulation with lamivudine, either alone or in combination with abacavir.

❖ **Adverse reactions:** Bone marrow suppression, anaemia and neutropenia, GI discomfort

❖ **Drug interactions:**

- Zidovudine + paracetamol: Both are metabolized by glucuronide conjugation → ↑ plasma concentration of zidovudine and its toxicity. .
- Azoles + zidovudine: Azole antifungal agents are hepatic microsomal enzyme inhibitors.
- Zidovudine + stavudine and ribavirin are activated by the same intracellular pathways

Antiviral drugs

2. Didanosine, Stavudine, Emtricitabine, Abacavir and Lamivudine

- Didanosine is a deoxyadenosine, absorption is effect by food and gastric Hcl (enteric coated)
- Stavudine is a thymidine analog, a strong inhibitor of DNA polymerases → reducing mitochondrial DNA synthesis and resulting in toxicity
- Emtricitabine, cytidine analogues, inhibits both HIV and HBV, is contraindicated in pregnancy and young children and in patients with hepatic or renal dysfunction.
- Abacavir, a guanosine analog, It is metabolized to inactive metabolites via alcohol dehydrogenase and glucuronyl transferase, and metabolites appear in the urine
- Lamivudine is a cytidine analoug, inhibits of both HIV and HBV. It is a commonly used agent in antiretroviral therapy because of its efficacy and low toxicity

❖ **The adverse effects:** peripheral neuritis, pancreatitis, gastrointestinal disturbances, lactic acidosis, skin rashes

B. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

❖ **Preparation:**

- Nevirapine, Efavirenz, (first-generation NNRTIs)
- Etravirine, Rilpivirine (second-generation, more active against resistant strains of HIV)

- Bind directly to reverse transcriptase enzyme and inhibit their function (Do not require intracellular phosphorylation to be active)
- Resistance from mutations, occurs very rapidly if these agents are used as monotherapy.
- They are used in combination with NRTIs in the treatment of AIDS

1. Nevirapine:

- It is used in combination with other antiretroviral drugs for HIV infections in adults and children, also in pregnant women with AIDS to prevent transmission of HIV virus to children
- Well absorbed orally. Cross CNS, placenta , and breast milk.
- It is an inducer of the CYP3A4, → drug interaction, such as oral contraceptives, ketoconazole and warfarin.

- **Adverse effects:** rash, fever, headache, and elevated serum transaminases and fatal hepatotoxicity

2. Efavirenz

- It is the preferred NNRTI, used in combination with other antiretroviral drugs for the treatment of HIV infections, a potent inducer of CYP450 enzymes

- **Adverse effects:** CNS toxicity, including (dizziness, headache, vivid dreams, and loss of concentration) and skin rash.

3. Etravirine

- It is a second-generation NNRTI active against many HIV strains that are resistant to the first-generation NNRTIs.
- The bioavailability of etravirine is enhanced with a high-fat meal.
- It is a potent inducer of CYP450

- **Adverse effect:** Rash, nausea, and diarrhea

4. Rilpivirine

- It is a second-generation NNRTI, approved for HIV treatment in combination with other antiretroviral agents.
- It is administered orally once daily with meals and acid gastric environment -dependent absorption
- It is primarily metabolized by CYP3A4, and drugs that induce or inhibit CYP3A4 may thus affect the clearance of rilpivirine.

- **Adverse effects**: rash, depression, headache, insomnia, and increased serum aminotransferases

NB: second-generation NNRTI, are higher potency, longer half-life and reduced side effect.

NB: Zidofudin , nevirapine are used in pregnant women with AIDS to prevent transmission of HIV virus to children

C. Protease Inhibitors (PIs)

As:, Ritonavir, Saquinavir, Indinavir, Nelfinavir,. atazanavir, darunavir .

- **M.O.A:** Inhibit HIV protease enzyme necessary for synthesis of mature proteins of virus coat → inhibit maturation of the viral particles and the production of noninfectious virions.
- High-fat meals → ↑ bioavailability of nelfinavir and saquinavir, whereas the bioavailability of indinavir is decreased, and others are essentially unaffected.
- **PIs** are used orally in combination with other HIV drugs (to avoid resistance) in patients with AIDS.
- **PIs** are extensively metabolized in liver. inhibitors of CYP3A4 (ritonavir having the most pronounced inhibitory effect) → Drug interactions
- Dosage adjustments are unnecessary in renal impairment.

❖ **Adverse effects**:

- Nausea, vomiting and diarrhea.
- Hyperglycemia and hyperlipidemia.
- Fat redistribution. (buffalo hump)

❖ **Drug interactions**: (potent Cyt450 inhibitor)

- with simvastatin or lovastatin,
- Excessive sedation from midazolam or triazolam,
- Respiratory depression from fentanyl.
- Also with warfarin, sildenafil, and phenytoin

D. Entry and Fusion Inhibitors:

As: Enfuvirtide and Maraviroc

Enfuvirtide

- Inhibitor of HIV fusion with the host cell.
- Binds with gp41 → prevent its fusion with host cell.
- Given SC in combination with other antiretroviral drugs.

- **Adverse effects** are related to the injection, pain, erythema, and nodules,

Maraviroc

- Chemokine receptor (CCR5) antagonist.
- Binds to CCR5 → blocking HIV protein (gp120) from associating with the receptor → prevent entry HIV through the cell membrane.
- Well absorbed orally and metabolized by CYP450 liver enzymes. (dose adjusted with other HIV drugs)

- **Adverse effects:** diarrhea, muscle and joint pain, and increases in hepatic transaminases

E. Integrase Inhibitors

As: Raltegravir ,elvitegravir, dolutegravir

- They inhibit integrase enzyme required for integration of DNA copy of RNA virus to host genome

- They are used orally in prophylactic and treatment of AIDS in combination with other agents eg lamivudine to reduce development of resistance.
- Metabolized by glucuronidation. (no interaction with CYP450 inducers or inhibitors)

- Dolutegravir is less effective than raltegravir

- Elvitegravir: Has more potent, prolonged action, less side effects, increased absorption by fatty diet. can be used alone with food or in combination with other

- **Adverse effects:** nausea, dizziness, fatigue and myopathy.

Antiviral infection

❑ Drugs used for treatment of HIV Infection

- In antiretroviral therapy (ART) regimen, consists of a combination of two NRTIs (e.g. tenofovir + emtricitabine or abacavir + lamivudine) combined with either an NNRTI (e.g. efavirenz) or a PI (e.g. atazanavir, darunavir) or raltegravir

❑ Drug regimen

- Zidovudine + Lamivudine + Efavirenz or
- Zidovudine + Lamivudine + Nevirapine or
- Tenofovir + Lamivudine + Efavirenz/Nevirapine

- **Prophylaxis of HIV infection (postexposure prophylaxis):** Zidovudine + Lamivudine, for 4 weeks

- **Drugs used to prevent transmission of HIV virus from mother to fetus are:** zidofudin + nevirapine, Tenofovir

Antiviral infection

- **Drugs used in treatment of influenza virus**:
  - **Oral oseltamivir** for mild cases for treatment of Bird Flu, Influenza A & B Influenza
  - **Zanamivir** for severe cases either inhaled or IV for treatment of Influenza A and B

- **Drugs used in treatment of Respiratory syncytial virus: Ribavirin**

- **Drugs used in treatment of herpes simplex virus infections**
  - Oral herpes simplex infection: **acyclovir** local ointment 5 % 5 times /day ..
  - Primary genital herpes: oral acyclovir or valaciclovir 1 g orally /12 hrs for 7–10 days.

- **Drugs used in treatment of cytomegalovirus**
  - **Ganciclovir** I.V., **DOC** for severe manifestations of CMV infection.
  - **Foscarnet** I.V. for resistant to ganciclovir or serious side effects from ganciclovir
  - Oral **valganciclovir** is used for CMV retinitis both for treatment and to prevent relapse.
  - **Cidofovir** IV or intravitreal is approved from treatment of CMV retinitis.

Drugs used in treatment of HBV infection

- **First line: Peginterferon α2a**
- **Second line**
  - **Tenofovir or enticavir :**
    - No or suboptimal response to interferone
    - In pregnant females with HBV or AIDS to prevent transmission to fetus .
    - Prophylactic against HBV within 72 hours of exposure.
- **Third line**: combination therapy: Lamivudine 100 mg once daily + tenofovir or enticavir

- **Drugs used in treatment of virus C infection(chronic active hepatitis):**
  - **Peginterferone 2α + ribavirin + Boceprevir or telaprevir.**

Antiprotozoal drugs

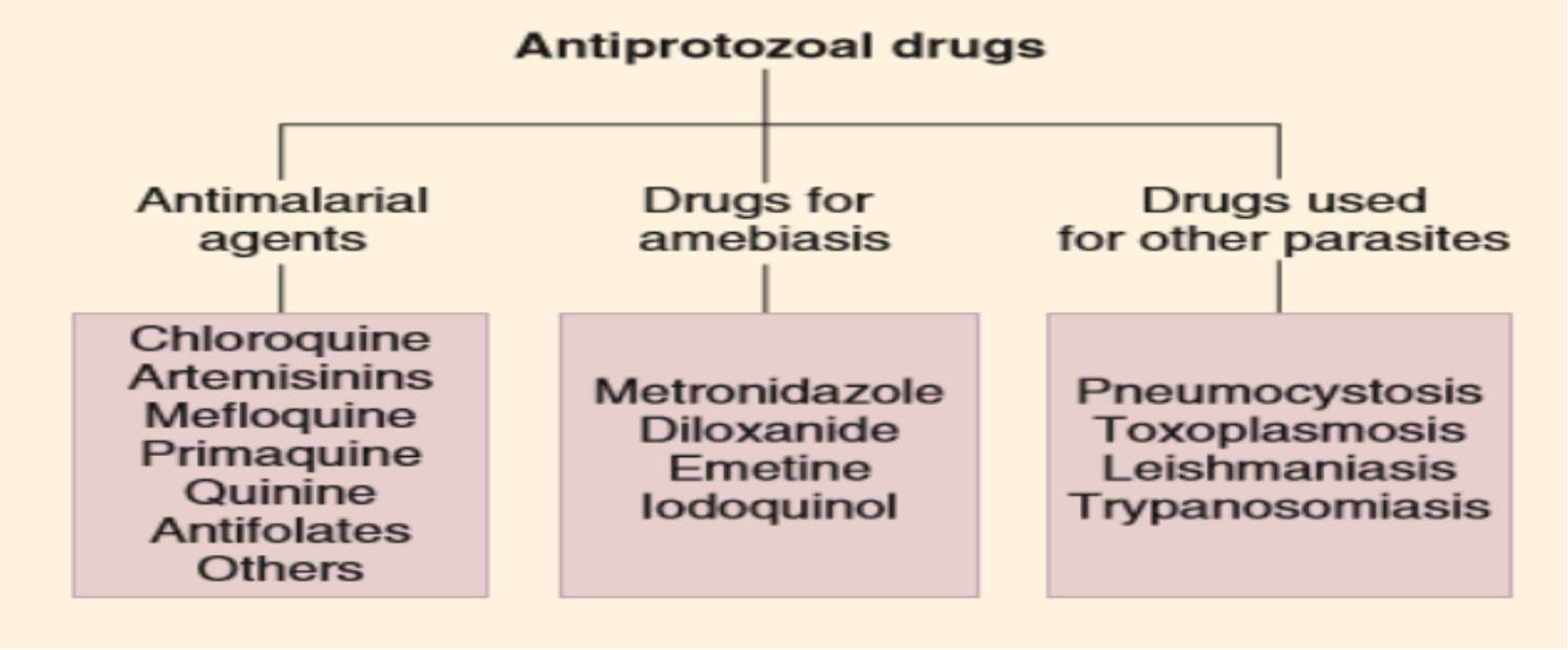
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Antiprotozoal Drugs

❖ **Antiprotozoal drugs** are used to treat protozoal infection which include:,

- **Amebiasis**
- **Malaria**
- **Toxoplasmosis**
- **Giardia**
- **leishmaniasis.**



Antiprotozoal Drugs

1. Amebiasis (amebic dysentery)

- Amebiasis is an infection produced by ingestion of cysts (non-invasive form) of E. histolytica. This organism can cause:

A. Bowel lumen amebiasis: Asymptomatic (carriers or cyst passers).

B. Tissue amebiasis: cysts develop into trophozoites which feed on intestinal or invade submucosa of large intestine, resulting in:

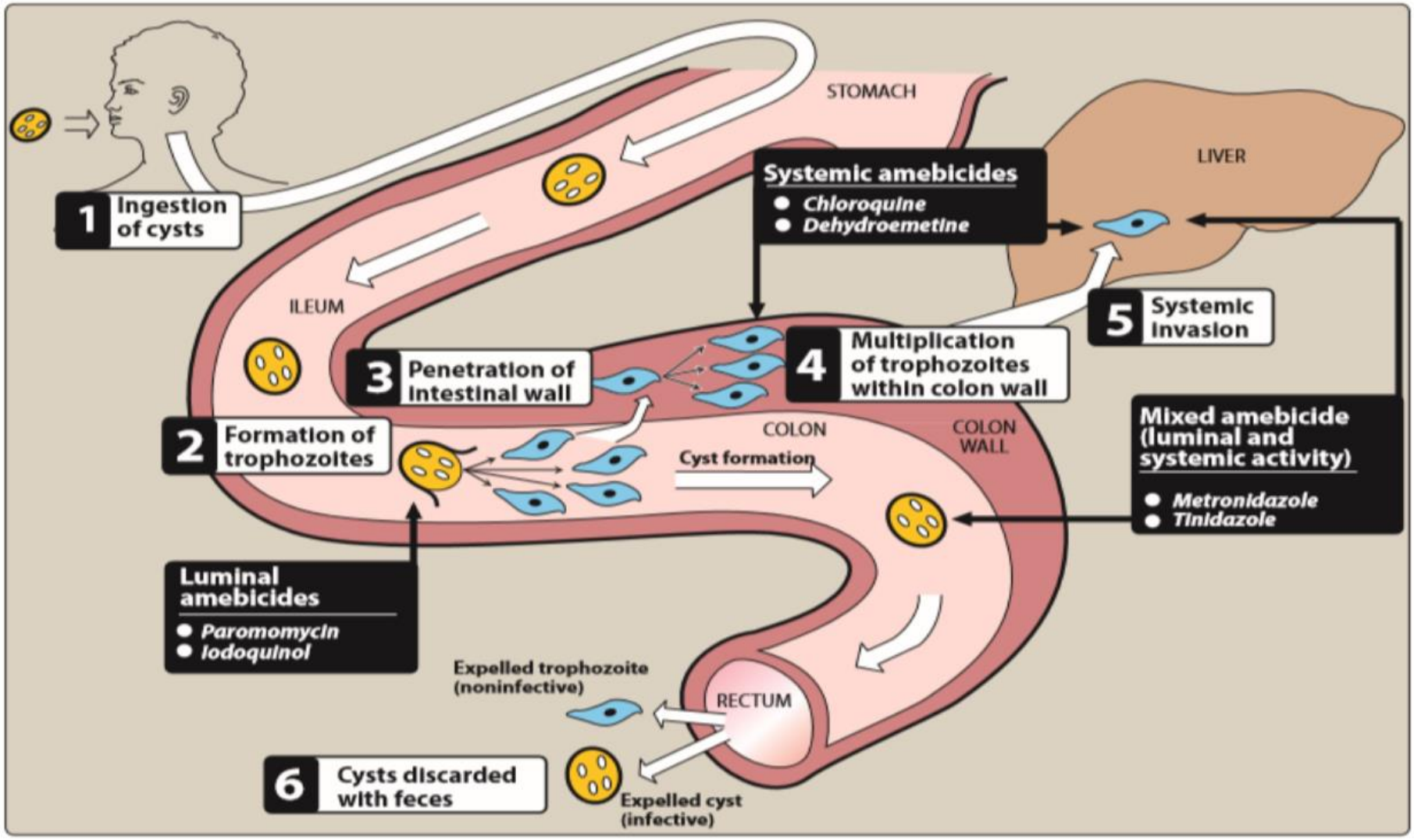
1. **Intestinal infection**: mild to moderate diarrhea or severe intestinal infection diarrhea with blood (dysentery). other (flatulence and abdominal cramps).

2. **Extra-intestinal amoebiasis**: liver abscess, pulmonary amoebiasis

❖ Classification of antiamebic drugs:

- **Luminal amebicides**: act in the lumen of the bowel and kill the cyst form (diloxanide, iodoquinol, paromomycin).
- **Systemic amebicides**: act in the intestinal wall and liver and kill trophozoites. (chloroquine, emetines)
- **Mixed amebicides**: effective against both the luminal and systemic and kill trophozoites (metronidazole, tinidazole).

Life cycle of Entamoeba histolytica



A. Mixed amebicides

Metronidazole (Flagyl)® -Tinidazole - secnidazole.

- Metronidazole, a nitroimidazole,. It kills trophozoites (but not cysts) and effectively (intestinal, extraintestinal and liver infections).

❖ Pharmacokinetics:

- Effective orally and distributed widely to tissue (Passes BBB& placental barrier. Concentrated in vagina, seminal fluid, breast milk and saliva.
- Metabolized by the liver (decreased in patients with impaired liver function) by cyt-p450
- Excreted mainly in the urine.

❖ M.O. A: cidal (bactericidal and amoebicidal)

- The nitro group of metronidazole reduced in anaerobic bacteria and sensitive protozoans → interacts with DNA and proteins → breakage of helical structure of DNA → cell death.

Antiprotozoal Drugs

❖ **Spectrum:** Amoeba (tissue more than luminal), Giardia, Trichomonas vaginalis, H. pylori and Anaerobic bacteria including Clostridium difficile.

❖ **Therapeutic uses:** 500 – 750 mg orally/8h for 5-10 days.

1- **Anaerobic protozoal infections:**

- **DOC:** Amoebiasis (all forms except asymptomatic cyst passers), giardiasis, Trichomonas vaginitis.

2- **Anaerobic bacterial infections:**

- Pseudomembranous colitis (**DOC**), acute ulcerative gingivitis, brain abscess, dental infections and H. pylori in peptic ulcer .

❖ **Adverse effects:**

- **GIT:** nausea, vomiting & metallic taste.
- **CNS**: Insomnia, vertigo, Dizziness, -ataxia- neuropathy
- **Disulfiram-like reaction with** alcohol
- **Teratogenic** (CI in pregnancy).
- **HME inhibitor** and decreases clearance of warfarin

2. Tinidazole & Secnidazole: :

- 2nd generation of nitroimidazole
- Similar to metronidazole but more effective, longer t ½ &less teratogenic → more suited for single dose or once daily therapy

- **Uses:** treatment of amebiasis, amebic liver abscess, giardiasis, trichomoniasis and H. pylori.

- **Dose:** Tinidazole : 2 g orally once daily with food (4 tab. 500 mg) for 3 days

Secnidazole: → a single 2 g dose → cure rates equal to multiple doses metronidazole and tinidazole

B. Luminal amebicides:

1. Diloxanide furoate

- Acts against trophozoites and cysts in intestine. Given orally
- Used for the treatment of asymptomatic amebiasis (**DOC) &** with metronidazole or tinidazole (tissue amebicide) in tissue amebiasis to eradicate source of infection. .
- **Side effects**: flatulence, nausea-abdominal cramps . Teratogenic
- **Dose**: 500 mg tid for 10 days

2. Iodoquinol

- Effective against luminal trophozoites and cysts.
- Used as an alternative to diloxanide for mild-severe intestinal infections. Also used in giardiasis.
- **Side effects**: rash, diarrhea and dose-related peripheral neuropathy

3. Paromomycin:

- Aminoglycoside antibiotic. Not absorbed from GIT. .
- Direct luminal amebicide alternative to diloxanide and indirectly by ↓ intestinal bacterial flora (nutrients for amebae). Effective also against in leishmaniasis
- GIT disturbances are the main side effect.

C. Systemic amebicides:

- Drugs used in the treating liver abscesses or intestinal wall infections caused by amebas

1) Chloroquine is an antimalarial drug, also used in combination with metronidazole to treat and prevent amebic liver abscesses. .
2) Emetine and dehydroemetine: alternative agents for the treatment of amebiasis (metronidazole-resistant amoebiasis).

Disease Form	Drug(s) of Choice	Alternative Drug(s)
Asymptomatic intestinal infection	Diloxanide furoate	Iodoquinol, paromomycin
Mild to moderate intestinal infection	Metronidazole *plus* luminal agent (see above)	Tinidazole, *or* tetracycline, *or* erythromycin *plus* luminal agent
Severe intestinal infection	Metronidazole *or* tinidazole *plus* luminal agent	Tetracycline *or* emetine *or* dehydroemetine *plus* luminal agent
Hepatic abscess and other extraintestinal disease	Metronidazole *or* tinidazole *plus* luminal agent	Emetine *or* dehydroemetine *plus* chloroquine (for liver abscess) *plus* luminal agent

Adapted, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 13th ed. McGraw-Hill, 2015.

2. Treatment of Giardiasis

1) Metronidazole: the **DOC** (250 mg TDs for 5 days)
2) Tinidazole : an alternative (2 g given once)
3) Nitazoxanide: used for the treatment of giardiasis, cryptosporidiosis (500 mg/12 h for 3 days).

3. Treatment of leshmaniasis:

1. Sodium stibogluconate is the first line agent for cutaneous and visceral leishmaniasis.

- Given intravenously (20 mg/kg/day) for 20-28 days.
- **Side effects**: GIT disturbances and cardiac arrhythmia.
- Given in caution with hepatic or renal dysfunction

- **Alternative agents include:** miltefosine (is the first orally active drug for visceral leishmaniasis), paromomycin, or fluconazole, metronidazole (for cutaneous lesions), and amphotericin B (for mucocutaneous leishmaniasis).

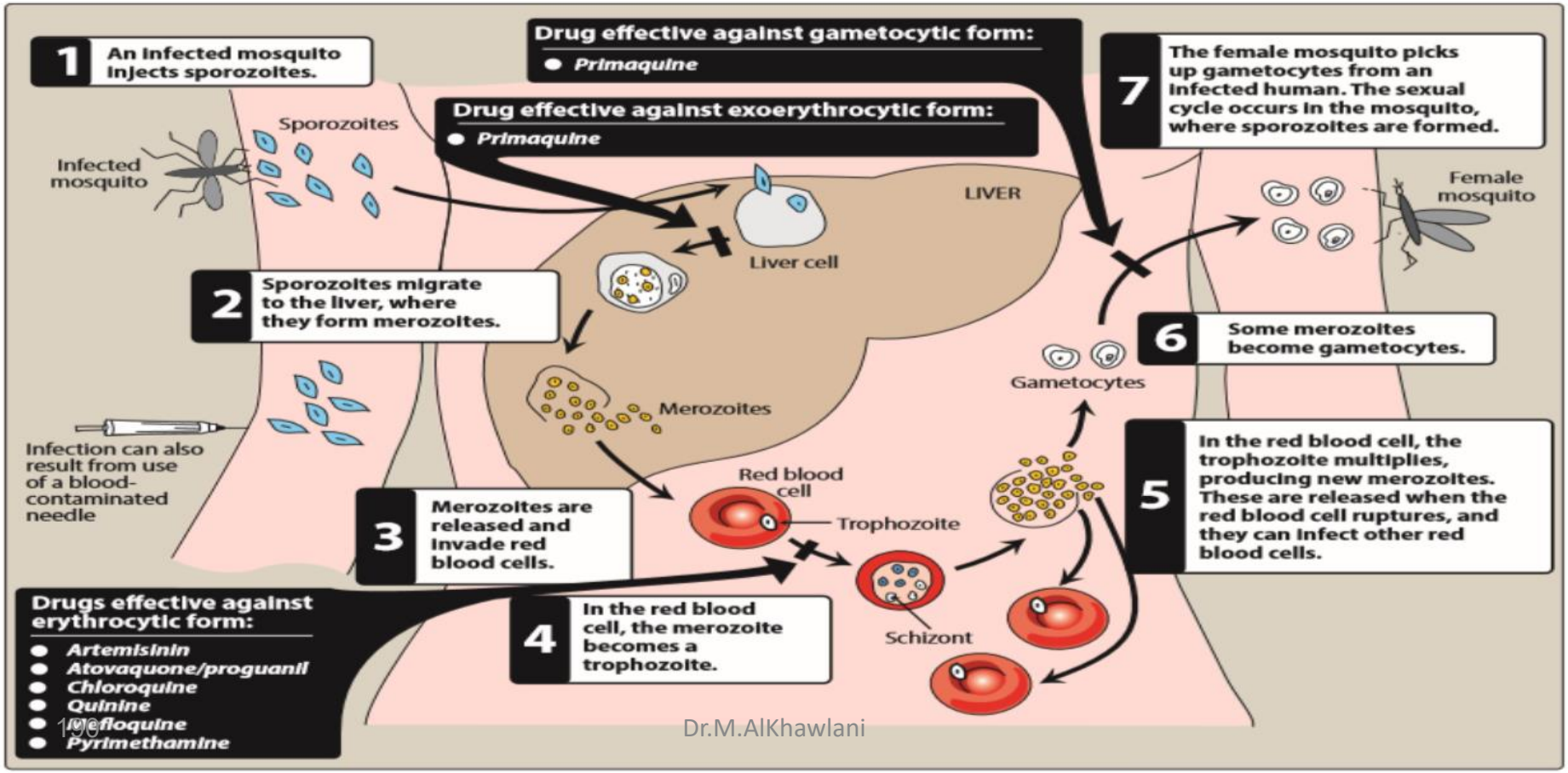
4. Treatment of toxoplasmosis

- Pyrimethamine + sulfadiazine (**DOC**). Acting as dihydrofolate reductase inhibitor.
- Pyrimethamine + clindamycin, or trimethoprim+ sulfamethoxazole, are alternative treatments.
- Trimethoprim/sulfamethoxazole is used for prophylaxis against toxoplasmosis in immunocompromised patients.
- Spiramycin can be used for toxoplasmosis in pregnant women.

5. Treatment of malaria

- Malaria is acute infectious disease caused by four species of plasmodium
  - **P. falciparum**: causing more severe infection and more resistant to drugs.
  - **P. vivax, P. ovale and P. malariae**: milder form of the disease.

- **Symptoms:** Persistent high fever, orthostatic hypotension, and massive erythrocytosis due to rupture of infected red blood cells (RBCs).


1 An infected mosquito injects sporozoites.
Sporozoites
Infected mosquito
Infection can also result from use of a blood-contaminated needle
2 Sporozoites migrate to the liver, where they form merozoites.
Drug effective against exoerythrocytic form:
Primaquine
LIVER
Liver cell
Merozoites
3 Merozoites are released and invade red blood cells.
Red blood cell
Trophozoite
4 In the red blood cell, the merozoite becomes a trophozoite.
Drugs effective against erythrocytic form:
Artemisinin
Atovaquone/proguanil
Chloroquine
Quinine
Mefloquine
Pyrimethamine
Schizont
5 In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells.
6 Some merozoites become gametocytes.
Gametocytes
Drug effective against gametocytic form:
Primaquine
7 The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.
Female mosquito

❖ Classification anti-malarial drugs according to the life cycle in the human host:

- **Erythrocytic schizonticides**: kill these forms only in erythrocytes. (eg, chloroquine, artemisinins, quinine)

- **Tissue schizontocides** (exoerythrocytic stages): act on pre-erythrocytic, as well as exoerythrocytic (P. vivax) stages in liver (eg, primaquine)

- **Gametocides**: kill gametocytes in blood → ↓ the transmission to mosquito, e.g. Primaquine).

A. Erythrocytic schizonticides:

1- Chloroquine: highly concentrated in infected RBCs

- The parasite digests host cell's haemoglobin → heme (toxic) and amino acids (essential for parasite), To protect itself, parasite polymerizes the heme to hemozoin.

- Chloroquine (weak base) → binds to heme and inhibits its conversion to hemozoin → drug – heme complex → oxidative damages plasmodial and RBC membranes → lysis of both the parasite and the RBC
- Resistance occurs by P. falciparum.

- A rapidly acting erythrocytic schizonticide against all species of plasmodia
- **Other actions of chloroquine**:
  1) Active against E. histolytica and Giardia lamblia
  2) Antiinflammatory, local anesthetic (on injection), weak smooth muscle relaxant
- Rapidly absorbed, given orally, IV & IM.
- Metabolized in the liver and slowly excreted in urine.

- **Therapeutic Uses:** (Category C)
  1. **For treatment of acute attack of malaria** caused by P. vivax, P. ovale, P. malariae and chloroquine-sensitive P. falciparum: **DOC**
  2. **For chemoprophylaxis**: for all types of malaria except chloroquine- resistant strains of P. falciparum (mefloquine or doxycycline can be used).
  3. **Other uses:** Amoebiasi, giardiasis, Rheumatoid Arthritis (hydroxychloroquine).

- **Adverse effects**:
  1. **Antimalarial doses** → nausea, vomiting, skin rashes, headache and visual disturbances.
  2. **Parenteral administration** → hypotension, confusion, convulsions, cardiac arrhythmias. Parenteral administration is better avoided or should be infused slowly.
  3. **long-term therapy** → ototoxicity, retinopathy, myopathy, neuropathy and rarely psychiatric disturbances → requires ophthalmological examination.

2- Mefloquine

- An effective drug for multi-resistant P. falciparum.
- Long acting blood shizonticide.
- Given orally for treatment and prophylaxis against all plasmodium species.
- Because of the potential for neuropsychiatric reactions, mefloquine is usually reserved for treatment of malaria when other agents cannot be used.

3- Quinine & Quinidine:

- Act as chloroquine.
- Given orally and by slowly IV infusion. (for about 3 hours)
- Quinine is highly active erythrocytic schizonticide against all plasmodium species, less effective and more toxic than chloroquine
- Used orally for uncomplicated chloroquine-resistant malaria, and IV for complicated/ cerebral malaria either chloroquine -sensitive or resistant
- Quinidine used as an antiarrhythmic & reserved for most chloroquine and multidrug resistant strains of P. falciparum

Adverse effects:

- Cinchonism (nausea, tinnitus, vertigo and blurred vision)
- Hypotension and cardiac arrhythmia. (following rapid IV).
- Hematologic changes, vertigo, and skin rash. Abortion due to oxytocic action.

4- Proguanil

- Inhibits plasmodial dihydrofolate reductase mainly through cycloguanil, its active metabolite, → inhibits folate production in both pre-erythrocytic and erythrocytic parasites → preventing DNA synthesis.
- **Current use** is restricted to prophylaxis of malaria in combination with chloroquine in areas of low level chloroquine resistance among P. falciparum.
- Can be employed during pregnancy.
- **Adverse effects:** nausea, vomiting, abdominal pain, headache, diarrhea, anorexia, and dizziness.

5- Artemisinin derivatives:

- Artemisinins are erythrocytic schizonticides active against P falciparum, including multidrug-resistant strains
- Given orally, parenterally and rectally. Metabolized in liver and excreted in the bile.
- The antimalarial action involves the production of free radicals resulting from cleavage of the drug's endoperoxide bridge by heme iron in the parasite food vacuole → toxic free radicals
- **Uses:**
  - Oral for the treatment of chloroquine and quinine-resistant strains. **DOC**
  - Parenterally: used in severe and complicated falciparum malaria
- **Side effects:** GIT disturbances and neurotoxicity .

Dr.M.Alkhawlani

B. Tissue schizonticides:

As: Primaquine

- Active against hepatic stages of malarial parasites. (including hypnozoites) of P. vivax and P. ovale. Also acts as gametocidal in all 4 types of malaria.
- Given in combination with blood shizonticides
- It is completely absorbed from the gut and rapidly metabolised in the liver, producing active compounds which causes hemolysis in G-6-PD deficiency

- **Clinical uses:**
  - Used after treatment with chloroquine or mefloquine, to eradicate P. vivax or P. ovale from the liver and prevent relapse, it is given orally for 15 days (15 mg /day).
  - Prevention of transmission: by killing the gametocytes in all 4 types of malaria.

- **Side effects:** GI tract disturbances, haemolysis in pts with G-6-PD deficiency
- Should be avoided during pregnancy, because fetus is G-6-PD deficient

C. Blood schizonticides and sporontocides

Pyrimethamine

- Inhibit dihydrofolate reductase leading to inhibition of folinic acid synthesis.
- Blood shizonticide and sporontocide in the mosquito`s gut, when the mosquito ingests it with the blood of the human host.
- Given orally &parenterally
- Combination of pyrimethamine with sulfadoxin (Fansidar)® is effective against P. falciparum, P. malariae to treat the acute attack of chloroquine-resistant malaria
- Combination of pyrimethamine with sulfadiazine is also used against toxoplasmosis.
- It is used for clinical cure and for prevention of transmission
- **Adverse effect**: GIT disturbances, megaloblastic anemia

Treatment and prevention of malaria.

All Plasmodium species except chloroquine-resistant P. falciparum

Chloroquine

Chloroquine-resistant P. falciparum

Atovaquone-proguanil, Artemether/lumefantrine

Alternate: *Mefloquine, Quinine plus: Doxycycline or clindamycin*

Prevention of relapses: P. vivax and P. ovale only

Primaquine

Prevention of malaria

Chloroquine-sensitive geographic areas

Chloroquine

Chloroquine-resistant geographic areas

Atovaquone-proguanil, Doxycycline, Mefloquine

In pregnancy

Chloroquine or mefloquine

Anthelmintic drugs

Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Anthelmintic drugs

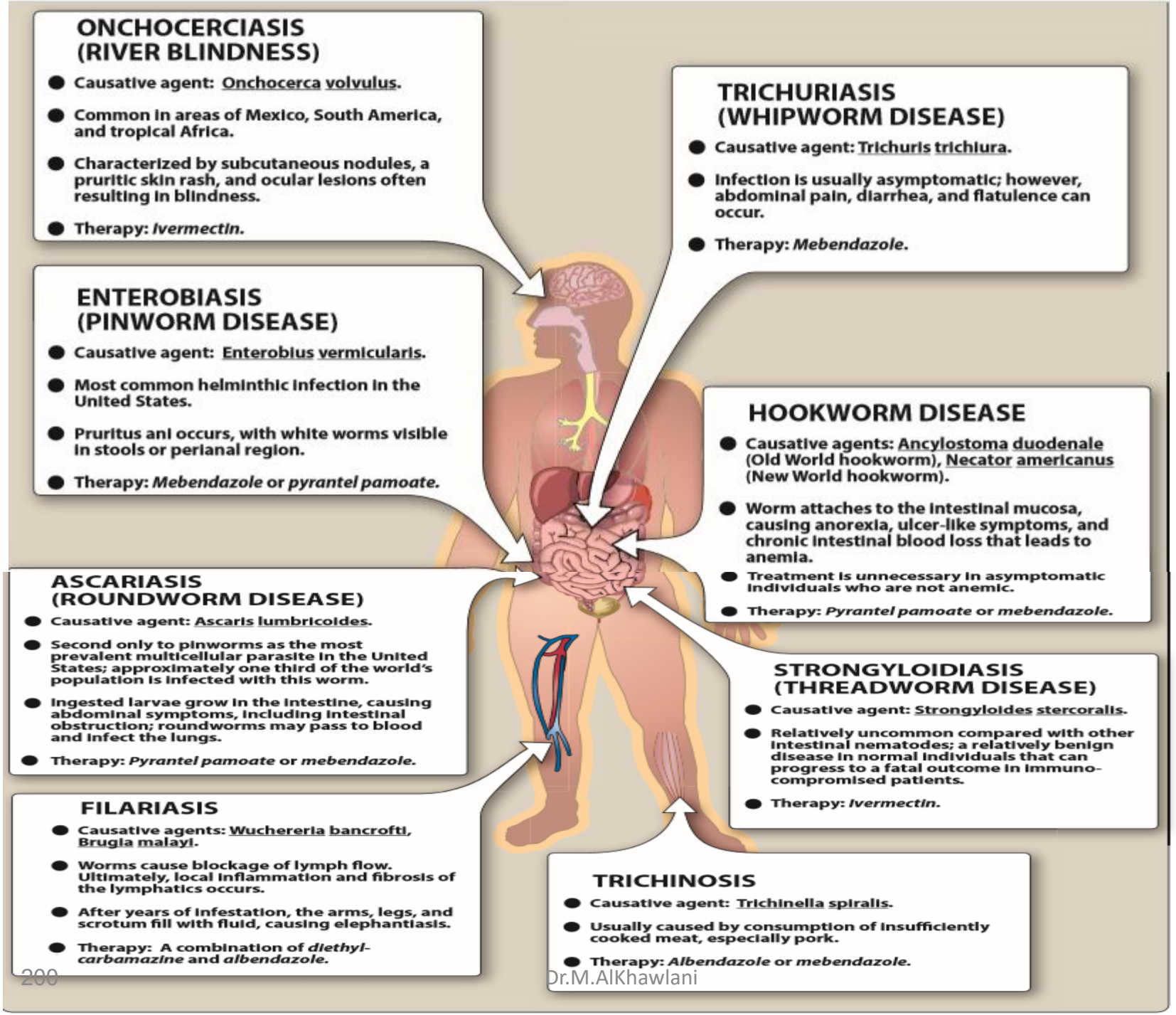
- Nematodes (round worms), trematodes (flukes), and cestodes (tape worms) are three major groups of helminths (worms) that infect humans

- **Anthelmintic drugs** are used to eradicate or reduce the number of helminths (worms) in the intestinal tract or tissues of the body.

❖ Drugs for the treatment of nematodes

- They cause infections of the intestine, blood and tissues.

Common name	Causative organism
1) Nematodes (Roundworms):	
Roundworm	Ascaris lumbricoides
Pinworm	Enterobius Vermicularis
Threadworm	Strongyloides Stercoralis
Hookworm	Ancylostoma duodenale, Necator americanus
Whipworm	Trichuris trichiura
Trichinosis	Trichinella Spiralis
Lymphatic Filariasis	Wuchereria Bancrofti and Brugia Species
Loiasis	Loa Loa
Onchocerciasis (river blindness)	Onchocerca Volvulus


ONCHOCERCIASIS (RIVER BLINDNESS)
Causative agent: Onchocerca volvulus.
Common in areas of Mexico, South America, and tropical Africa.
Characterized by subcutaneous nodules, a pruritic skin rash, and ocular lesions often resulting in blindness.
Therapy: Ivermectin.
TRICHURIASIS (WHIPWORM DISEASE)
Causative agent: Trichuris trichiura.
Infection is usually asymptomatic; however, abdominal pain, diarrhea, and flatulence can occur.
Therapy: Mebendazole.
ENTEROBIASIS (PINWORM DISEASE)
Causative agent: Enterobius vermicularis.
Most common helminthic infection in the United States.
Pruritus ani occurs, with white worms visible in stools or perianal region.
Therapy: Mebendazole or pyrantel pamoate.
HOOKWORM DISEASE
Causative agents: Ancylostoma duodenale (Old World hookworm), Necator americanus (New World hookworm).
Worm attaches to the intestinal mucosa, causing anorexia, ulcer-like symptoms, and chronic intestinal blood loss that leads to anemia.
Treatment is unnecessary in asymptomatic individuals who are not anemic.
Therapy: Pyrantel pamoate or mebendazole.
ASCARIASIS (ROUNDWORM DISEASE)
Causative agent: Ascaris lumbricoides.
Second only to pinworms as the most prevalent multicellular parasite in the United States; approximately one third of the world's population is infected with this worm.
Ingested larvae grow in the intestine, causing abdominal symptoms, including intestinal obstruction; roundworms may pass to blood and infect the lungs.
Therapy: Pyrantel pamoate or mebendazole.
STRONGYLOIDIASIS (THREADWORM DISEASE)
Causative agent: Strongyloides stercoralis.
Relatively uncommon compared with other intestinal nematodes; a relatively benign disease in normal individuals that can progress to a fatal outcome in immuno-compromised patients.
Therapy: Ivermectin.
FILARIASIS
Causative agents: Wuchereria bancrofti, Brugia malayi.
Worms cause blockage of lymph flow. Ultimately, local inflammation and fibrosis of the lymphatics occurs.
After years of infestation, the arms, legs, and scrotum fill with fluid, causing elephantiasis.
Therapy: A combination of diethyl-carbamazine and albendazole.
TRICHINOSIS
Causative agent: Trichinella spiralis.
Usually caused by consumption of insufficiently cooked meat, especially pork.
Therapy: Albendazole or mebendazole.

❖ Drugs for the treatment of nematodes

- **Preparation:** Benzimidazoles (Mebendazole, Albendazole, Thiabendazole), Diethylcarbamazine, Ivermectin,, Pyrantel pamoate,

1. Mebendazole (Vermox®): Broad spectrum anthelmintic

- Inhibits parasitic microtubule synthesis and glucose uptake → depletion of energy → slowly death of the worm or clearance outside GIT with feces.
- Absorption from intestine is minimal, 75-90% of an oral dose is passed in the faeces.

- **Active against (1st choice in)** : ascaris (roundworm), ancylostomiases (hookworm), enterobius (pinworm), Trichuris (whipworm). → Useful in :
  - **Enterobiasis:** single 100-mg orally once as single dose, repeated after 2& 4 weeks.
  - **Other nematode infections**: 100mg twice daily for 3 days,

- **Adverse effects** include abdominal pain and diarrhea.
- **Contraindicated** in pregnancy

2. Flubendazole is an analog of mebendazole but also effective in strongyloidiasis .

Anthelmintic drugs

3. Albendazole (Zentel)®: broad spectrum for nematodes & cestodes

- Same action as Mebendazole.
- Moderate absorption after oral administration (food →↑ its absorption)
- Broad spectrum effective against nematodes (ascaris, ancylostomiases, enterobius, Trichuris) and cestodes infection (as Cysticercosis and hydatid disease)

- **Dose:**

  - **For nematodes**: Single oral dose 400mg with meal (repeat for 3 days for ascaris & in 2wks for enterobius, Oxyuris).
  - **for hydatid disease**: 400 mg bid for 3 months
  - **1st choice for neurocysticercosis**: 400 mg bid for 21 days plus corticosteroids to minimize the immune reaction of parasites.

- **Adverse effect** after long term therapy: Abdominal pain & headache. Nausea& vomiting Hepatotoxicity.
- **Contraindicated** in pregnancy.

4. Thiabendazole: Effective against strongyloidiasis and early stages of trichinosis

- Same action as Mebendazole. .
- Because of its toxic effects, thiabendazole is an alternative to Ivermectin in strongyloidiasis (threadworm).

- **Side effects:** Nausea, vomiting, abdominal pain, diarrhoea, loss of appetite, headache, drowsiness and dizziness (most common) .
- **Contraindicated** in pregnancy

5. Pyrantel Pamoate:

- Acts as a depolarizing N-M blocker & ↓cholinesterase → Spastic paralysis of worm. Active against: Ascaris, Ancylostomiasis & enterobius (Oxyuris) but NOT Trichuris.
- Poorly absorbed orally
- **Uses:** Alternative to mebendazole in ancylostoma, ascaris & enterobius.
- **Dose:**10 mg /kg single dose (repeated after two weeks)
- **Adverse effects:** GIT disturbances, Headache and drowsiness,

6. Ivermectin:

- Acts by activating glutamate-gated chloride channel receptors → ↑ chloride influx and hyperpolarization → paralysis of the worm.
- It is given orally and does not readily cross the BBB.
- **Uses:** 1st choice for strongyloidiasis, and onchocerciasis (river blindness)
- **Adverse effects:** fever, headache, dizziness, rashes, tachycardia, hypotension, and pain in joints, and muscles.
- **Contraindicated** in pregnancy.

7. Diethylcarbamazine

- Drug of choice in the treatment of filariasis combined with albendazole
- It causes paralysis of microfilaria and alters their surface structure, making them more susceptible to destruction by host defense mechanisms
- Absorbed after oral ingestion, Distributed all over the body, Metabolized in liver and excreted in urine

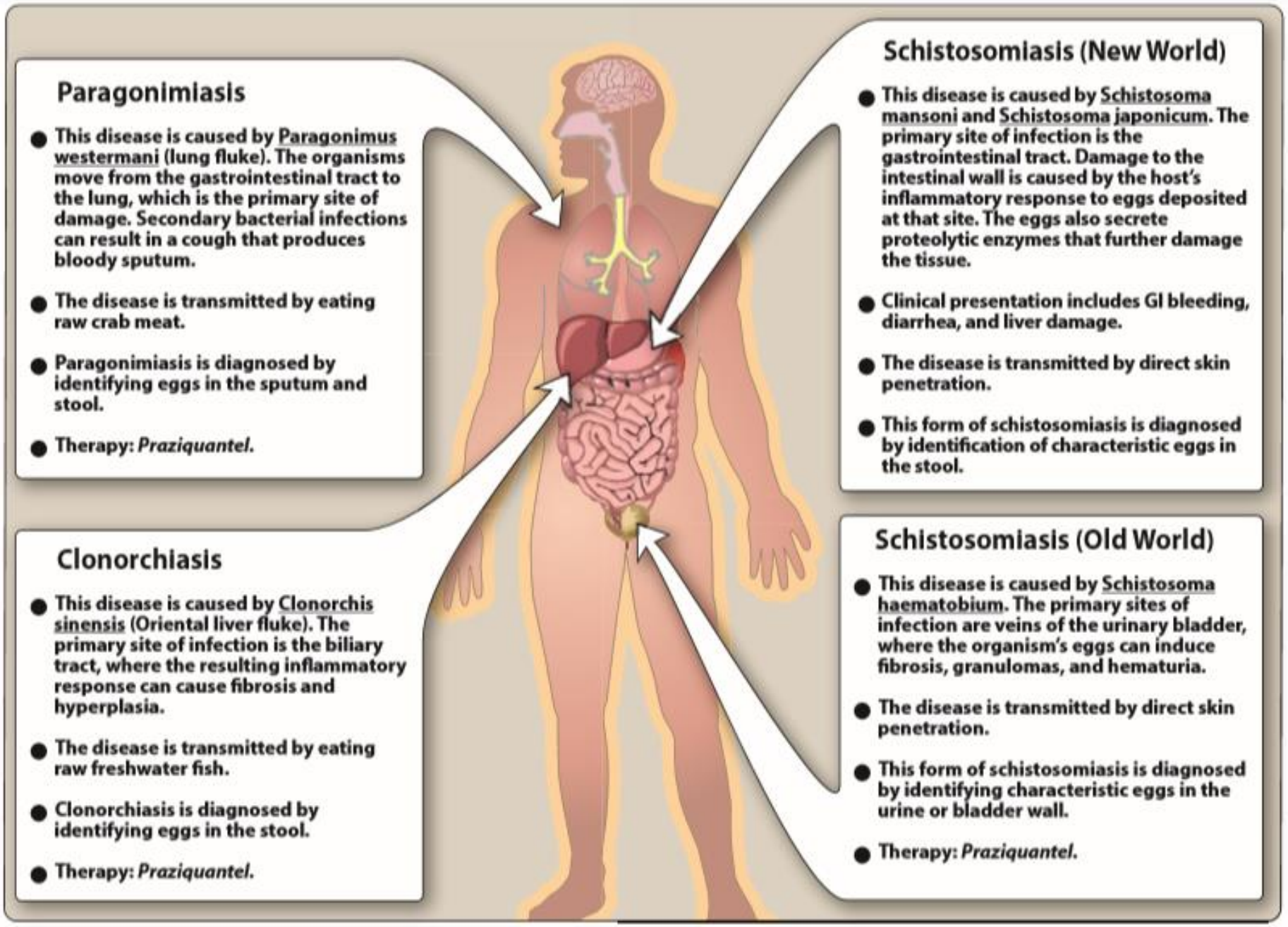
- **Side effects:**

- Allergic manifestations due to killing large number of microfilariae (Antihistaminics or corticosteroids are used routinely in the first 4-5 days of treatment)
- Anorexia, nausea, vomiting & headache.

2. Drugs for the treatment of trematodes: (flukes) are leaf-shaped flatworms

- They cause infections of tissues (for example, liver, lung, intestinal, or blood)

Type of flukes	Site of infestation	Drug of 1st choice	Drug of 2nd choice
Schistosoma haematobium (bilharziasis)	Urinary bladder	Praziquantel	Metrifonate
Schistosoma mansonia (bilharziasis)	Large intestine	Praziquantel	Oxamniquine
Paragonium	Lung	Praziquantel	Albendazole
Heterophysis heterophysis	Small intestine	Praziquantel	Albendazole
Chonoichus &opisthorchus	Liver	Praziquantel	Albendazole
Fasciola beski	Liver	Praziquantel	Albendazole


Paragonimiasis
This disease is caused by Paragonimus westermani (lung fluke). The organisms move from the gastrointestinal tract to the lung, which is the primary site of damage. Secondary bacterial infections can result in a cough that produces bloody sputum.
The disease is transmitted by eating raw crab meat.
Paragonimiasis is diagnosed by identifying eggs in the sputum and stool.
Therapy: Praziquantel.
Schistosomiasis (New World)
This disease is caused by Schistosoma mansoni and Schistosoma japonicum. The primary site of infection is the gastrointestinal tract. Damage to the intestinal wall is caused by the host's inflammatory response to eggs deposited at that site. The eggs also secrete proteolytic enzymes that further damage the tissue.
Clinical presentation includes GI bleeding, diarrhea, and liver damage.
The disease is transmitted by direct skin penetration.
This form of schistosomiasis is diagnosed by identification of characteristic eggs in the stool.
Clonorchiasis
This disease is caused by Clonorchis sinensis (Oriental liver fluke). The primary site of infection is the biliary tract, where the resulting inflammatory response can cause fibrosis and hyperplasia.
The disease is transmitted by eating raw freshwater fish.
Clonorchiasis is diagnosed by identifying eggs in the stool.
Therapy: Praziquantel.
Schistosomiasis (Old World)
This disease is caused by Schistosoma haematobium. The primary sites of infection are veins of the urinary bladder, where the organism's eggs can induce fibrosis, granulomas, and hematuria.
The disease is transmitted by direct skin penetration.
This form of schistosomiasis is diagnosed by identifying characteristic eggs in the urine or bladder wall.
Therapy: Praziquantel.

Anthelmintic drugs

1. Praziquantel: broad-spectrum for trematodes & cestodes)

- Acts by ↑cell membrane permeability to calcium → ↑ contraction and paralysis of the worm.
- Rapidly absorbed (food →↑its absorption) Distributed all over the body and extensively metabolized.

❖ Therapeutic uses

- **1st choice** in schistosomiasis (bilharziasis, in all species) 40 mg/kg single oral dose or 20 mg/kg 3 doses in one day
- For other trematodes**.** e.g. liver flukes, Paragonimus
- **Effect also** in some cestodes infections
  - Taeniasis **(**T. saginata, T. solium, and H. nana): 1st choice (single dose of 5-10mg/kg).
  - Neurocysticercosis: 2nd choice to albendazole plus corticosteroids.
  -Hydatid disease as an adjunct to albendazole pre-and post-surgery.

- **Adverse effects:** dizziness, headache, gastrointestinal upset. Teratogenic (CI in pregnancy)
- Drugs that inhibit cytochrome P450 causing ↑ praziquantel level.

❑ Alternative drugs for bilharziasis:

Oxamniquine: used for S. mansoni infection → Large intestine

Metrifonate: used for S. hematobium infection. → Urinary bladder

3. Drugs for the treatment of cestodes (tapeworm): Praziquantel, niclosamide, albendazole

1. Niclosamide:

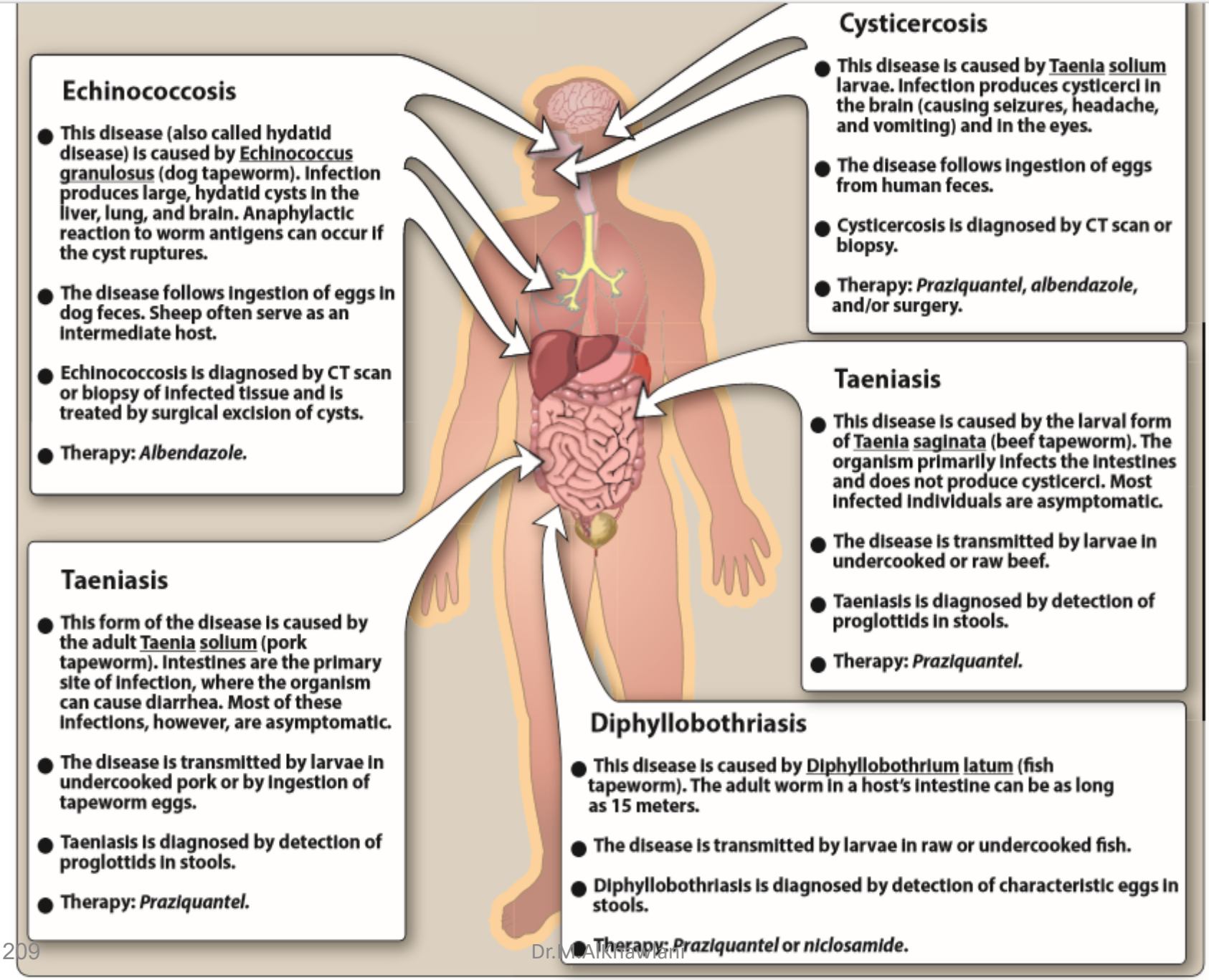
- It inhibits the generation of ATP by preventing phosphorylation of ADP in mitochondria →↓ energy production → worm death.
- It is kill adult worm (but not ova). Purgatives are usually given after niclosamide to remove viable ova and dead segments from the gut. (ova may lead to cysticercosis)

- 2nd line to praziquantel for most tapeworm.
- It is not effective in **cysticercosis** (albendazole or praziquantel is used) or hydatid disease caused by Echinococcus granulosus (for which albendazole is used).

❖ **Dose for tapeworm**: 2g (4 chewed tablets),single dose on empty stomach.

❖ **Adverse effects:** GIT distress, headache, rash, and fever.

- Safe during pregnancy and in pts with poor health


Cysticercosis
This disease is caused by Taenia solium larvae. Infection produces cysticerci in the brain (causing seizures, headache, and vomiting) and in the eyes.
The disease follows ingestion of eggs from human feces.
Cysticercosis is diagnosed by CT scan or biopsy.
Therapy: Praziquantel, albendazole, and/or surgery.
Echinococcosis
This disease (also called hydatid disease) is caused by Echinococcus granulosus (dog tapeworm). Infection produces large, hydatid cysts in the liver, lung, and brain. Anaphylactic reaction to worm antigens can occur if the cyst ruptures.
The disease follows ingestion of eggs in dog feces. Sheep often serve as an intermediate host.
Echinococcosis is diagnosed by CT scan or biopsy of infected tissue and is treated by surgical excision of cysts.
Therapy: Albendazole.
Taeniasis
This disease is caused by the larval form of Taenia saginata (beef tapeworm). The organism primarily infects the intestines and does not produce cysticerci. Most infected individuals are asymptomatic.
The disease is transmitted by larvae in undercooked or raw beef.
Taeniasis is diagnosed by detection of proglottids in stools.
Therapy: Praziquantel.
Taeniasis
This form of the disease is caused by the adult Taenia solium (pork tapeworm). Intestines are the primary site of infection, where the organism can cause diarrhea. Most of these infections, however, are asymptomatic.
The disease is transmitted by larvae in undercooked pork or by ingestion of tapeworm eggs.
Taeniasis is diagnosed by detection of proglottids in stools.
Therapy: Praziquantel.
Diphyllobothriasis
This disease is caused by Diphyllobothrium latum (fish tapeworm). The adult worm in a host's intestine can be as long as 15 meters.
The disease is transmitted by larvae in raw or undercooked fish.
Diphyllobothriasis is diagnosed by detection of characteristic eggs in stools.
Therapy: Praziquantel or niclosamide.

Anthelmintic drugs

Drugs for the treatment of helminthic infections

Infecting Organism	Drugs of Choice	Alternative Drugs
Nematodes		
Ascaris lumbricoides (roundworm)	Albendazole *or* mebendazole *or* pyrantel pamoate	Ivermectin, piperazine
Necator americanus and *Ancylostoma duodenale* (hookworm)	Pyrantel pamoate *or* albendazole *or* mebendazole	
Trichuris trichiura (whipworm)	Albendazole *or* mebendazole	Ivermectin
Strongyloides stercoralis (threadworm)	Ivermectin	Albendazole, thiabendazole
Enterobius vermicularis (pinworm)	Mebendazole *or* pyrantel pamoate	Albendazole
Trichinella spiralis (trichinosis)	Mebendazole (+/– corticosteroids)	Albendazole
Cutaneous larva migrans	Albendazole *or* ivermectin	Thiabendazole
Wuchereria bancrofti and *Brugia malayi* (filariasis)	Diethylcarbamazine	Ivermectin
Onchocerca volvulus (onchocerciasis)	Ivermectin	
Trematodes (flukes)		
Schistosoma haematobium	Praziquantel	Metrifonate
Schistosoma mansoni	Praziquantel	Oxamniquine
Schistosoma japonicum	Praziquantel	
Paragonimus westermani	Praziquantel	Bithionol
Fasciola hepatica (sheep liver fluke)	Bithional *or* triclabendazole	
Fasciolopsis buski (large intestinal fluke)	Praziquantel *or* niclosamide	
Cestodes (tapeworms)		
Taenia saginata (beef tapeworm)	Praziquantel *or* niclosamide	Mebendazole
Taenia solium (pork tapeworm)	Praziquantel *or* niclosamide	
Cysticercosis (pork tapeworm larval stage)	Albendazole	Praziquantel
Diphyllobothrium latum (fish tapeworm)	Praziquantel *or* niclosamide	
Echinococcus granulosus (hydatid disease)	Albendazole	

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تجميع: محمد مروان-البوت العلمي الصيدلاني

Autacoids (Local hormones)



Dr. Mohammed Al-Khawlani

Assist. Professor of pharmacology and Toxicology

Autacoids

- The word ‘autacoids’ comes from the Greek words: ***autos*** (self) & ***akos*** (medicinal agent or remedy or cure).
- Autacoids are produced by cells or tissues and act locally. Hence, they are also called ‘local hormones’.
- They are Diverse (Heterogeneous) substances have different structures and pharmacological activities, with biologic activity. Released in response to various stimuli,

❖ **Autacoids are classified according to their chemical structure into:**

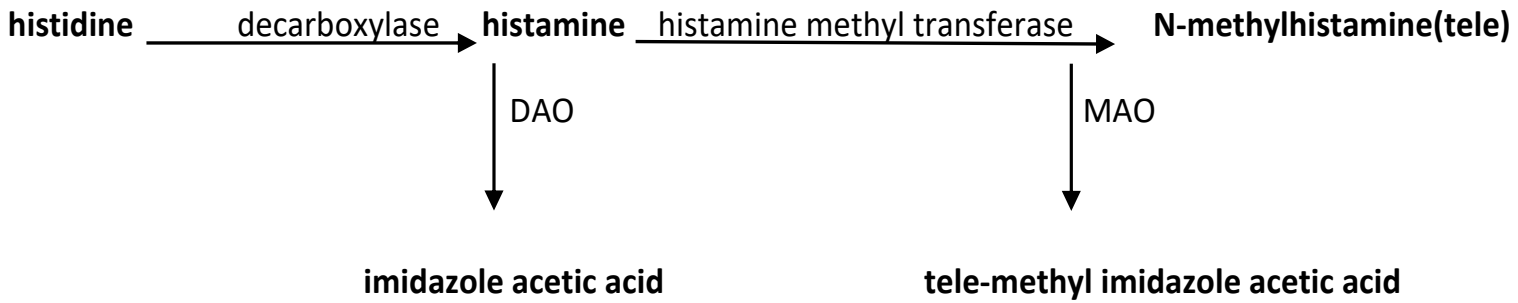
- Amino acid derivatives e.g histamine and 5-hydroxy tryptamine (serotonin).
- Endogenous peptides e.g kinins, angiotensin, substance P, vasoactive intestinal polypeptide (VIP) and atrial natriuretic factor (ANF).
- Fatty acid derivatives e.g eicosanoids and platelet activating factors.

Autacoids

Histamine:

❑ Synthesis and metabolism:

It is synthesized by decarboxylation of the amino acid, histidine.

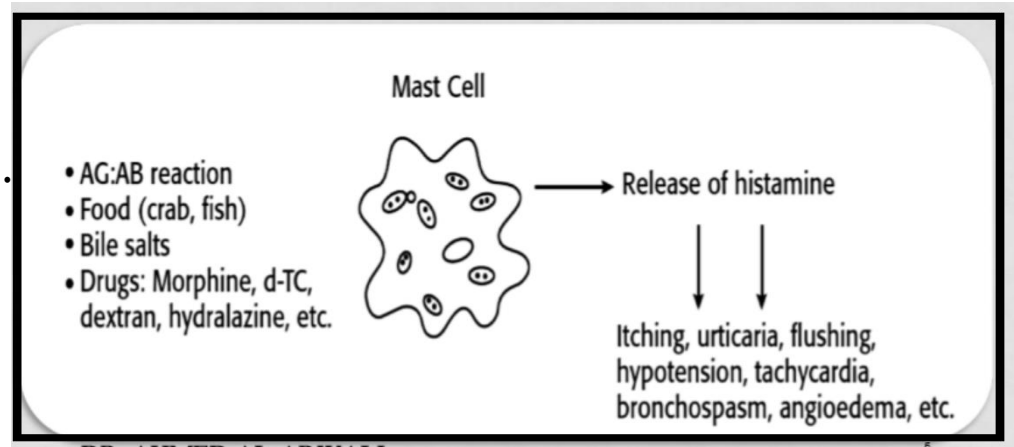


❑ Storage: in high concentrations in:.

- Mast cells (lung, skin, GIT, BV…etc
- Basophiles, Platelets, Enterochromaffin- like (ECL) cells of the stomach
- Brain

❑ Released in cases of

- Antigen-antibody reactions (allergy).
- Destruction of cells (Inflammation).
- Some drugs morphine and curare


Mast Cell
• AG:AB reaction
• Food (crab, fish)
• Bile salts
• Drugs: Morphine, d-TC, dextran, hydralazine, etc.
Release of histamine
Itching, urticaria, flushing, hypotension, tachycardia, bronchospasm, angioedema, etc.

Histamine

❑ Mechanism of action and effects of histamine

- Histamine exerts its effects by binding to histamine (H) receptors. (specific cellular histamine receptors)

Type	Location	Function
H_1 histamine receptor	Found on smooth muscle, endothelium, and central nervous system tissue	-Causes vasodilation (edema, hypotension and may lead to anaphylactic shock -Bronchospasm & increase GIT motility. Stimulation of salivary ,lacrimal, GIT secretion (allergic rhinitis symptoms) . Redness, pain and itching. - In C.N.S vomiting, vertigo and motion sickness.
H_2 histamine receptor	Located on parietal cells	Primarily stimulate gastric acid secretion
H_3 histamine receptor	Found on central nervous system and to a lesser extent peripheral nervous system tissue	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin

❑ Histamine antagonist by:

- Physiological antagonism (e.g., Adrenaline). Inhibit the release of histamine (e.g., cromolyn). H-receptors blocker (H1-H2 blocker)

❖ H1- receptor antagonists: (Antihistaminic drugs)

First generation	Second generation
-Pass to the brain (pass blood brain barrier)	-No
-They cause sedation	No
-They relieve vomiting (antiemetic effect)	No
-They treat motion sickness	No
-Atropine like action (blurring of vision , dryness of secretion , dry mouth , constipation and urinary retention	No
-Antiallergic , antiproctatic	Antiallergic , antiproctatic
Therapeutic uses: - Antiallergic(treatment of allergy , antiproctatic(treatment of itching) - Antiemetic -Antidiarrheal due to atropine like action -Sedative -Antimotion sickness -Treatment of common cold البردbecause they decrease nasal and bronchial secretion by H1 blockade and atropine like action	**Therapeutic uses** - Antiallergic(treatment of allergy , antiproctatic(treatment of itching) -They can be used topically

Side effects -Sedation in therapeutic doses due to H1 blockade -CNS stimulation(hallucination and convulsions) in toxic doses due to atropine like action -Teratogenic if used during pregnancy (meclizine & cyclizine)	**Side effects** -Cardiac arrhythmia in large doses -Drug allergy -Cetirizine produces mild sedation because it partially passes to the central nervous system
Preparations: **-Diphendyramine , dimenhydranate** : potent sedatives and atropine like action **-Promethazine** : potent sedatives and atropine like action+ alpha adrenergic blocker (postural hypotension) -Chlorpheneramine , bromopheneramine , clemastine: moderate sedation -Meclizine , cyclizine : very mild sedation	**Preparations** -Loratidine -Cetirizine -Fexofenadine & desloritidine : more potent and less cardiac arrhythmia عدم انتظام ضربات القلب

❖ H2- receptor antagonists: (Antihistaminic drugs)

- Act mainly on GIT by blocking H2 receptors → decrease secretion of gastric acids (HCl and pepsin) and decrease gastric motility.

❑ Therapeutic uses:

- Peptic ulcer.
- Gastroesophageal reflux disease. (GERD) (Heart burn)
- Zollinger- Ellison Syndrome.

❑ Drugs:

- **Cimetidine** (Tagamet)® (400mg bid or 800mg at bedtime).
- **Ranitidine** (Zantac)® (150mg bid or 300mg at bedtime)
- **Famotidine** (Pepcid)® (20mg bid or 40mg at bedtime)
- **Nizatidine** (Axid)® (150mg bid or 300mg at bedtime)

  - Given orally and parenterally.
  - Famotidine is the most potent.
  - Cimetidine is not widely used due to dangerous side effects

❑ Side effects with cimetidine:

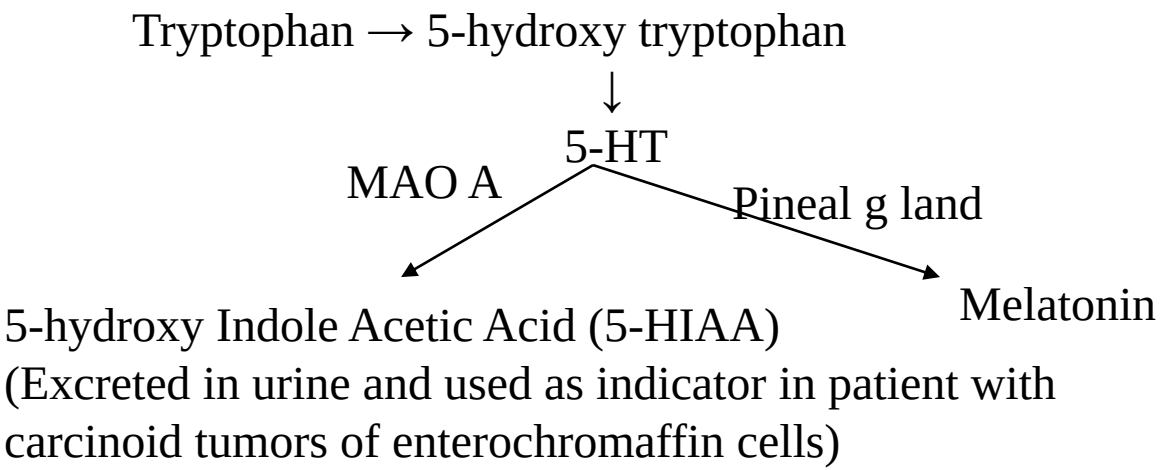
- Anti-androgenic action→ impotence.
- ↑ Prolactin → gynaecomastia in men and galactorrhoea in women.
- CNS disturbances → confusion.
- Hepatic microsomal enzyme inhibitor→ ↑ action of other concomitant drugs.

- Side effects of other H2-blockers occurring in less than 3% of patients including diarrhea, headache and fatigue.

Serotonin

Serotonin (5-hydroxy tryptamine): (5-HT)

❑ Synthesis:


Tryptophan → 5-hydroxy tryptophan
5-HT
MAO A
Pineal g land
Melatonin
5-hydroxy Indole Acetic Acid (5-HIAA)
(Excreted in urine and used as indicator in patient with carcinoid tumors of enterochromaffin cells)

❑ **Found in** high concentration in CNS, GIT (synthesis and storage) and platelets (storage only).

❑ **Actions of serotonin:** The main receptors which mediate the action of serotonin are:

- **5-HT1 receptors:**
  5-HT1D, 5-HT1B: stimulation causes cerebral vasoconstriction.
  5-HT1A: stimulation causes anti-anxiety action.

- **5-HT2 receptors**:
  Stimulation causes CNS induction, suppression of appetite, general vasoconstriction and . smooth muscle contraction, Hallucinations

Serotonin

- **5-HT3 receptors**:
  Found in CTZ. Stimulation causes nausea, vomiting and pain.

- **5-HT4 receptors**:
  Found in GIT. Stimulation causes spasms and ↑ gastric emptying.

❑ Examples of serotonin receptor agonists:

- **Buspirone:**
  - Selective 5-HT1A agonist (partial agonist)
  - Used orally (5,10mg tab.) to treat anxiety with or without depression.
  - Delay onset of action. (1-2 weeks)

- **Sumatriptan:** (Imigran)®
  - Selective 5-HT1D & 5-HT1B agonist.
  - Used orally, parenterally and intranasal in acute migraine.
  - More effective than ergotamine.
  - Nausea, chest pain and coronary vasospasm are the main side effects.
  - Contraindicated in pregnancy and peripheral vascular diseases.

Serotonin

- **Ergotamine:**
  - 5-HT1D partial agonist.
  - Also act as a partial agonist on α1-receptors → VC.
  - Treats acute migraine (orally & parenterally).
  - Nausea is the common adverse effect.
  - May combined with caffeine (Cafergot)® or cyclizin (Migril)®.
  - Contraindicated in pregnancy and peripheral vascular disease.

- **Ergometrine:** (Methergine)®
  - 5-HT2 & α1 partial agonist.
  - Stimulates uterine smooth muscle contraction → oxytocic action.
  - Used also for treatment and prevention of postpartum hemorrhage.
  - Given orally and parenterally.

- **Metoclopramide**: (Plasil)®
- **Domperidone**: (Motilium)®
  - Selective 5-HT4 agonists → ↑ GIT motility and used for treatment of nausea & vomitin
  - Act centrally by blocking 5-HT3 & D2 receptors in CTZ → ↓ nausea and vomiting.
  - Metocloperamide acting centrally more than domperidone.
  - Given orally and parenterally.

Serotonin

- **Selective serotonin reuptake inhibitors**: (SSRIs)
  - Lead to ↑ serotonin action.
  - As: Fluoxetin (Prozac)® Sertralin (Zoloft)® Cetalopram (Cipram)®
  - Used orally as antidepressant drugs.

❑ Examples of serotonin receptor antagonists:

- **Cyproheptadin**: (Periactin)®
- **Pizotifen**: (Mosegor)®
  - 5-HT2 receptors antagonists.
  - Used as appetizer, in allergy (H1-blocker) and for prophylaxis of migraine.
  - Sedation and dry mouth are the main side effects.

- **Ondansetron & Granistron**:
  - Selective 5-HT3 blockers.
  - Used orally and parenterally for prevention and treatment of nausea & vomiting associated with surgery and cancer chemotherapy.
  - Headache is the common side effect.

- **Ketanserin:**
  - Selective 5-HT2 blocker.
  - Causes mixed VD and prevent platelet aggregation.
  - Also has selective blocking for α1, H1 and dopamine receptors.
  - Used for treatment of hypertension and peripheral vascular diseases.

❑ Management of migraine:

- Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with nausea, vomiting and sensitivity to light, sound or smell. (neurovascular disorder)

- Migraine may be preceded with aura (classical migraine) or without aura (common migraine).

- **Treatment during attack:** (depends on the severity)
  - Analgesics: as NSAIDs (Ibuprofen or paracetamol with caffeine)
  - Ergotamine.
  - Triptans: as sumatriptan. Antiemetics: as metocloperamide. Sedatives: as diazepam.

- **For prophylaxis:** (between the attacks)
  - Anti-serotonin drugs: as methysergide, cyproheptadine and pizotifen.
  - Propranolol. (most common)
  - Calcium channel blockers. (As flunarizine)
  - Antidepressant drugs: as fluoxetine.
  - Clonidine.
  - Corticosteroids. (As dexamethasone)

Drugs used for Cough

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cough

- It is a protective reflex which helps to expel secretions and other irritant materials from the respiratory airways.

❖ Causes of cough:

➢ The sensitivity of cough reflex is increased by:

- bronchial asthma, chronic bronchitis , lung fibrosis
- Reflux esophagitis, allergic rhinitis
- Upper & lower respiratory tract infection
- drugs (angiotensin converting enzyme inhibitors , PGE analogues

❖ Classification of cough

- **Acute:** sudden onset/less than 3 weeks
- **Sub-acute:** 3-8 weeks
- **Chronic:** more than 8 weeks

cough

Types of cough

Dry cough	Productive or useful (wet) cough
No sputum. Respiratory mucous is very little and very sticky to be removed by coughing	Excessive respiratory mucous that stimulate cough reflex
Reaction to irritant **Acute** : smoking , dust , allergin **Chronic** (increase sensitivity of cough reflex by chronic asthma , esophageal reflex , sinusitis or drugs(angiotensine converting enzyme inhibitors.	Reaction to inflammation , infection **Acute** : common cold , bronchitis , pneumonia **Chronic**: chronic obstructive airway disease , chronic infection(TB).
Usually associated with itchy sensation in the throat ,headache , dizziness	Usually associated with fever and fatigue , chest pain due to fatigue of respiratory muscles
Treated with suppression of cough reflex by antitussive drugs	Treated by either • Encouraging cough reflex by expectorants • Decrease surface tension of sputum by **surfactants** • Change the chemical structure of sputum by **mucolytic**

Dry cough

1. Antitussive drugs (cough suppressant):

- Drugs that suppress cough by a direct inhibition on the cough center & used in dry cough.

❖ Classification:

a) Centrally acting antitussive drugs: ↓cough center in the medulla.

1- Opiate: Codeine, Pholcodeine.

2- Non-Opiate: Benzonatate, Butamirate

3- Antihistamine: Chlorpheniramine, diphenhydramine

b) Peripherally acting: ↓ afferent arc (Stretch receptors)

1- Stop smoking

2- Benzonatate

3- Demulcents

4- Steam inhalation

- Used only for dry, unproductive cough and dangerus cough
- Central antitussives are contraindicated in productive cough BUT Expectorants and mucolytics can be used in dry cough

Antitussive drugs (Dry cough)

Narcotic opioids:

1. Codeine: Category c

- ❑ It is natural Opium Alkaloid, with weak opioid agonist
- ❑ It is more selective for cough center, it stimulates μ (mu) and δ (Sigma) opiate receptors → ↓ cough center.
- ❑ Less than Morphine as Analgesic, Constipating, Addicting.

❖ Therapeutic use:

- ❑ Treat dry cough. dose (10-20 mg/ 6 h.)
- ❑ Analgesic in Mild or Moderate pain + Aspirin + Paracetamol

❖ Side effects:

- ❑ Addiction, constipation, urinary retention,
- ❑ At high dose respiratory depression, itching due to histamine release.

❖ Contraindicated

- ❑ Asthmatics

Antitussive drugs (Dry cough)

2. Pholcodeine: Category A

- It is an opioid antitussive with mild sedative effect.
- Has little or no addictive, analgesic & constipating properties.
- Similar efficacy as antitussive to codeine
- Long acting than codeine (12 h)
- Dose: 5-15 mg orally.
- It is safe for pregnancy

Antitussive drugs (Dry cough)

Non- narcotic opioids:

1. **Noscapine** (X):

- ❑ It is a non-narcotic alkaloid derived from opioid
- ❑ Depresses cough but has no narcotic, analgesic or dependence inducing properties
- ❑ Useful in spasmodic cough.
- ❑ Dose: 15-30 mg/6 h..

❖ **Side effect:** ❑ Headache & nausea can occur.

2. **Dextromethorphan** (C)

- ❑ A synthetic compound
- ❑ **They stimulate** σ(Sigma) opiate receptors and inhibits NMDA (N-methyl D-aspartate) glutamate receptors.
- ❑ It is similar to codeine with no analgesic action
- ❑ Produces less constipation than codeine and no CNS depressant.
- ❑ Antitussive action for 6 hours.
- ❑ Dose: 15-30mg three or four times daily

❖ **Side effects:** ❑ Dizziness, nausea & drowsiness

Antitussive drugs (Dry cough)

Antihistamines

- H1 blocker (1st generation) drugs are used as antitussives.
- They relieve cough due to their sedative and anticholinergic actions, but lack selectivity for the cough center.
- They may reduce secretions by anticholinergic action
- Useful in allergic cough.
- Have no expectorant property.
- Added to antitussives/expectorant formulation
- **Chlorpheniramine** (2-5 mg), **Diphenhydramine (B)** (15-25 mg) , **Promethazine** (15-25 mg) are commonly used.
- 2nd generation drugs cannot cross BBB, they are ineffective as antitussive

Antitussive drugs (Dry cough)

❖ **Peripheral antitussives:** ↓ Cough Stretch receptors along respiratory tract.

1- Benzonatate:

- ❑ Chemically related to Procaine, which is local anesthetic.
- ❑ Dual Antitussive Central (Cough center) + Peripheral (Cough "Stretch" receptors).
- ❑ local anesthetic that inhibit stretch receptors in respiratory tract.
- ❑ Oral dose: 100 -200 mg TID.

❖ **Side effects:**

- ❑ dry mouth, hypersensitivity reaction,
- ❑ overdose produces convulsions, cardiac arrhythmia.

2- Pharyngeal demulcents: (lozenges or syrup)

- ❑ As: Honey, glycerin and liqurice.
- ❑ Reduce afferent arc from the irritated mucosa & sooth throat
- ❑ They provide relief to dry cough arising from throat.

Antitussive drugs (Dry cough)

3- Steam inhalation with benzoin and menthol

- ❑ They ↑ bronchial glands to secret→ Thin, soothing & protective mucus.
- ❑ Used in tracheo-bronchitis.

4- Stop Smoking → Treat smoker's cough.

Expectorant & mucolytic drugs

A) Expectorants:

- Drugs which ↑ bronchial secretions or reduces viscosity (liquefy sputum) facilitating its removal by coughing

- **They are divided into:**

a. Sedative expectorant:

- As: Ipecacuanha, Ammonium chloride, Ammonium bicarbonate. Potassium Iodide, Sodium or Potassium citrate.

b. Stimulant expectorants:

- **As:** Guaiphenesin, creosote and terpene hydrate

Expectorant & mucolytic drugs

❖ Sedative expectorant:

- ❑ Sedate the acutely inflamed mucosa.
- ❑ ↑ Secretions of thin and hydrated mucous

1- Na &K acetate, benzoate, bicarbonate.

- ❑ They are metabolized in the body to bicarbonates which cause alkalosis, excess alkali is excreted by bronchial glands which dissolve thick sputum →Easy productive expectoration
- ❑ Useful in Bronchitis & Bronchial asthma

2- Epecacuanha or ammonium chloride

- ❑ Oral administration in sub-emetic dose → gastric irritation and reflex irritation to respiratory system →↑ bronchial secretion.
- ❑ Overdose causes vomiting, gastritis
- ❑ Useful in Bronchitis & Bronchial asthma

Expectorant & mucolytic drugs

3- Na or K iodides

- Secreted by bronchial gland →↑ bronchial secretion → liquefying sputum.
- They are used in chronic bronchitis.

❖ **Side effect:**

- Allergy.,
- Iodism: nausea, vomiting, metallic (bitter) taste, salivation, conjunctivitis, lacrimation, rhinitis.

❖ **Contraindications:**

- Acute bronchitis (irritation causes more inflammation)
- Pregnancy: iodine may interfere with fetal thyroid function.

4-Steam inhalation(water vapor) which liquefies sputum.

Expectorant & mucolytic drugs

- **Stimulant expectorants:**
  - **As: Guaifenesin.**
    - It is beneficial in treatment of cough:
      - Expectorant: by increasing volume and decrease viscosity of mucous by direct stimulation of bronchial glands.
      - Antitussive by reducing cough reflex through inhibition of excitatory NMDA glutamate receptors
    - Mild analgesic through NMDA receptor blockade
    - Guaifenesin, an expectorant, is available as a single-ingredient formulation and is also a common ingredient in combination products with codeine or dextromethorphan.
    - **Adverse effects**: Gastric disturbances and drowsiness.

Expectorant & mucolytic drugs

B) Mucolytic:

- Drugs that decrease viscosity of sputum by changing its chemical structure
- They ameliorate productive cough by facilitation of removing of sputum
- They are used in treatment of productive cough and male infertility to increase sperm motility

1. Acetylcysteine: & methylcytine, carboxymethylcystin & erdosteine .

- Contain free SH group which break disulfide bonds in mucus.
- They are given orally, inhalation, or injection.
- Acetylcysteine has antioxidant action→ anti-inflammatory action
- Carboxymethylcystine has additional surfactant action that decrease surface tension of sputum

❖ **Uses:**

- Mucolytic in acute and chronic pulmonary diseases as T.B., pneumonia, and cystic fibrosis.

Expectorant & mucolytic drugs

2. Bromhexine and Ambroxol:

- Bromhexine: It breaks down polysaccharide bonds of sputum
- Ambroxol: analgesic to respiratory passages, increase synthesis of natural surfactant and breaks down polysaccharide bond of sputum.
- Ambroxol is more effective than bromohexine.
- Bromohexine oral dose: 4-8 mg tid, safe for pregnancy
- Ambroxol oral dose: 15-30 mg tid.
- Can be given orally, parenterally and by inhalation
- Mucolytics are useful also in bronchitis and bronchial asthma

Expectorant & mucolytic drugs

❖ Surfactants

As: Calfactant alfa

- ❑ They decrease surface tension of sputum which facilitates expulsion

- ❑ It is natural surfactant used in treatment of chronic respiratory distress syndrome

Bronchial asthma Therapy

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Bronchial asthma

- It is a chronic inflammatory disease of airways characterized by increased bronchial responses to a variety of stimuli (allergic stimuli) which leads to acute attacks of bronchospasm, excessive mucous secretion and congestion of bronchial mucous membrane.

❖ **Symptoms**:

- shortness of breath, cough (nocturnal cough), chest tightness, wheezing, and rapid respiration.

❖ **Pathogenesis of bronchial asthma:**

1- On the first exposure to a specific antigen in genetically predisposed persons, synthesis of lgE occurs.
2- **Early phase reaction**: On 2nd exposure to allergens causes interaction between IgE and antigen with release of inflammatory mediators (histamine, leukotrienes) and interleukins from sensitized lymphocytes. This causes bronchospasm, increased mucous secretion (acute attacks).
3- **Late phase reaction:** On repeated exposure to allergens causes more intense attacks due to memory cell stimulation. Chronic bronchial inflammation due to overproduction of leukotriene, growth factors
4- **End stage:** Irreversible bronchospasm, hypertrophy of bronchial muscles and goblet cells, bronchial fibrosis.

❖ **Factors Precipitating Asthma:**

- Allergy (pollen, dust, mites, grass, …. etc).
- exercise,
- Smoking.
- After viral or bacterial chest infections.
- Emotional stress.
- Some drugs like NSAIDs -Non-Selective B-Blockers-Morphine-Muscarinic agonists-ACE inhibitors -histamine releasers (as Curare and Trimetaphan), beta blockers or NSAIDs.

❖ **Drug Therapy in Bronchial Asthma:**

a) **Bronchodilators** (Short-term asthma relievers):
- Sympathomimetic B2-Agonists e.g. Salbutamol
- Methylxanthines e.g. Theophylline.
- Antimuscarinic drugs (Muscarinic antagonists) e.g. lpratropium

b) **Anti-inflammatory drugs** (Long-term asthma controllers):
- Mast cell stabilizers e.g. Di-Sodium Cromoglycate.
- Leukotriene antagonists: Montelukast & Zileuton
- Glucocorticoids e.g. Hydrocortisone.

N.B.: Anti-inflammatory drugs are not bronchodilators and are not used in acute attacks of bronchial asthma, but used for prophylaxis.

1. Sympathomimetics

- **P.K:**
  - They are non-catecholamines: absorbed orally-pass BBB and not metabolized by COMTor MAO.

- **Mechanism of action**
  - Stimulation of bronchial β2 receptors → ↑ cAMP → bronchodilatation.
  - Stimulation of β2 receptors in the mast cells → ↓ histamine release

Preparation:

1. **Selective β2 agonists:**

- **Short acting (SABA):** (duration 3-4 h)
  - Salbutamol (Ventolin)®, terbutaline →Rapid onset of action (15-30 minutes).
    Oral dose: 2 - 4 mg bid - Inhalation dose:100µg/puff/6 hours (Salbutamol) & Oral dose: 2.5 mg tid (Terbutaline)
- **Long acting (LABA):** (duration 12 h)
  - Salmeterol and formoterol → Slow onset
    Given by inhalation only as aerosol spray or inhalant powder. Dose:25-50 µg/puff/12 hours (Salmeterol) & 12 µg/puff/12 hours (Formoterol)

Therapeutic uses in bronchial asthma:

1- The drugs of choice in acute attacks: SABA are given by inhalation.
2- LABA are given for long-term prophylaxis with inhaled steroids.
3- Salbutamol is given by inhalation (nebulizer) or IV in severe acute asthma (status asthmaticus).

Adverse effects:

1- Tremors, Tachycardia, Tolerance
2- Hypokalemia.
3- Hypotension-Headache-Flushing.

2. **Non-selective β-receptor agonists:**
   - They are not commonly used because of cardiac adverse effects as tachycardia, palpitation, arrhhythmia and anginal pains due to B1-stimulation. Examples:

• Adrenaline (inhalation and S.C.).
• Isoprenaline (inhalation and S.L.).

2) Methylxanthines:

Preparation: Theophylline and Aminophylline (theophylline ethylenediamine)

Pharmacokinetics:

- Theophylline is given orally as "sustained release" preparations (SR) and Aminophylline is given as rectal suppository or IV administration.
- Pass BBB.
- Metabolized by HME.

Mechanism of action:

1- Inhibition of phosphodiesterase enzyme (PDE) → ↑ intracellular cAMP:
   - In smooth muscle → Relax bronchial smooth muscles (bronchodilation) and mast cell stabilization.
   - In smooth muscle →↑cardiac contraction.
2- Block of adenosine receptors:
   - In smooth muscle →bronchodilation,
   - In brain: CNS stimulation. (as alertness, nervousness and insomnia).
   - In smooth muscle →↑cardiac contraction

Therapeutic uses in Bronchial asthma:

1- In acute asthmatic attacks resistant to β2 agonists: Slow IV Aminophylline 250-500 mg.
2- Prophylaxis of bronchial asthma: Theophylline is given as sustained release tablets or capsules (100-300mg/12 hours) for long term control of asthma.
3- Status asthmaticus: IV injection or infusion of aminophylline in combination with corticosteroids.
4- In chronic obstructive pulmonary disease.

Side effects:

- Theophylline and Aminophylline have low therapeutic index and the plasma level should be measured to avoid toxicity, Therapeutic plasma concentration: 5-20 mg / L and the toxic level > 20 mg / L.
- CNS stimulation**:** nervousnss, insomnia, headache, and seizures (convulsions).
- Cardiac stimulation leading to tachycardia, arrhythmia and hypotension
- Nausea & vomiting

Drug Interactions of Theophylline:

1. Metabolic enzyme inhibitors as Cimetidine, Erythromycin & Quinolones and Heart & Hepatic Diseases → ↓ metabolism of theophylline → ↑ the action.
2. Metabolic enzyme inducers as Rifampicine, Phenobarbitone, Phenytoin & Carabamazepine and Tobacco (Heavy smokers) & Alcohol → ↑ metabolism of theophylline → ↓ the action.

3. Anti-muscarinic drugs:

- Atropine was previously used in prophylaxis of bronchial asthma but is now replaced by synthetic substitutes.
  Examples: lpratropium -Oxtropium -Tiotropium

Mechanism of action:

- They are competitive antagonists that block muscarinic receptors in bronchi by competition with acetylcholine released as a result of vagal stimulation

1. Ipratropium bromide:

- Synthetic Quaternary Ammonium Compound → NOT Orally & NOT pass BBB.
- Causes bronchodilation without drying of bronchial secretions.
- Slow onset of action. (1-2 hours)
- Used by Inhalation in Prophylaxis of asthma & COPD

2. Oxtropium -Tiotropium:

- Synthetic Quaternary ammonium compound similar to lpratropium but:
  - More potent (10 times) & Longer duration

Therapeutic uses in Bronchial asthma:

- They are given by inhalation in prophylaxis of bronchial asthma& COPD
- They may be added to B2 agonist to achieve synergism.

4. Mast Cell stabilizers

Preparation:

- **Specific: Only act as mast cell stabilizers**
  - Disodium cromoglycate: (Cromolyn); 20 mg capsule inhaled by special inhaler or 10% solution by nebulizer or eye drops 0.02% .
- **Nonspecific: They have other actions:**
  - Ketotifen 1 mg tablets or 0.025% solution. It has H1 ,5HT, leukotriene antagonist. It cross blood brain barrier. It causes sedation

Mechanism of action:

- Inhibit the release of inflammatory mediators from mast cells → stabilizing of mast cells → anti-inflammatory & anti-allergic action.
- They have no effect on bronchial muscles or antigen antibody reaction.

Therapeutic uses in Bronchial asthma:

- Prophylactic before exposure to triggering agents (exercise, irritants, NSAIDS, aspirin induced asthma).
- Treatment of allergic skin diseases eg urticaria, allergic rhinitis, allergic conjunctivitis as topical preparation.
- Prevention (prophylactic) of irritant induced cough (angiotensin converting enzyme inhibitors, bradykinin).

N.B: They are ineffective in treatment of acute attacks of bronchial asthma because they have no bronchodilator effects

Adverse effects:

- Bronchospasm, cough, chest tightness, throat irritation, dry mouth.
- Ketotifen may cause drowsiness.

5. Corticosteroids:

Preparation:

-Hydrocortisone - Prednisolone and Methyl prednisolone (Depo-Medrol)®
-Betamethazone - Beclomethasone (Becotide)®
-Dexamethasone -Fluticasone - Budesonide

- Budesonide, fluticasone, mometasone have low systemic toxicity due to hepatic metabolism
- Fluticasone furoate is long acting used once daily.

Mechanism of action corticosteroids in asthma:

- Acting by inhibition of phospholipase A2 → ↓ arachidonic acid synthesis → inhibit leukotriene, prostaglandins synthesis → broad anti- inflammatory action.
- Prevent antigen/antibody reaction.
- Mast cell stabilization → ↓ release of mediators.
- ↓ Vasodilatation and edema of bronchi.

Therapeutic uses in bronchial asthma:

1- **Inhaled corticosteroids** (ICS) as Beclomethasone, Fluticasone, Triamcinolon, Budesonide, are used in prophylaxis of bronchial asthma.
   - This is the preferred route to avoid the serious adverse effects of systemic steroids (immunosuppression-osteoporosis-edema-hypertension-ulcer …).

2- **Systemic steroids** as Hydrocortisone sodium succinate or methylprednisolone **IV** is the drug of choice in status asthmaticus (200 mg./ 4-6 hours for 24 hours).

- This is followed by oral prednisolone for 7-10 days then gradually withdrawn to avoid acute adrenocortical insufficiency.

3- **Systemic steroids** as prednisolone orally are used only in severe persistent asthma not responding to other anti-asthmatic drugs

Adverse effects of Inhaled steroids:

1- Oro-pharyngeal candidiasis (moniliasis): prevented by mouth wash after corticosteroid inhalation, and treated by oral Nystatin.
2- Dysphonia (voice abnormality, e.g. weakness and hoarseness).
3- Systemic adverse effects may occur on prolonged use, e.g. growth retardation in children and osteoporosis in females

Adverse effects of long term therapy:

5- Hypertension. (Na and water retention)
6- Euphoria and psychosis. (elevation of mood)
7- Peptic ulcer. (↑ gastric secretion)
8- Glaucoma and cataract.
9- Osteoporosis. (↓ Ca absorption from GIT and ↓ osteoblasts formation)
10- Hyperglycemia. (↓ insulin release and ↑ gluconeogenesis)
11- ↑ Risk of infection. (immune-suppressive action)

- Inhaled corticosteroids have fewer side effects than oral or parenteral forms.
- Withdraw gradually after long term therapy.

Contraindicated in pregnancy and lactation.

6. Leukotriene antagonist:

Preparation:

- **Leukotriene synthesis blockers:** Zileuton 600 mg twice daily
- **Leukotriene receptor blockers: Zafirlukast**:20 mg twice daily, **Montelukast** 4 mg in children, 10 mg in adult once daily

Mechanism of action:

1- Inhibition of 5-Lipooxygenase and inhibition of leukotrienes synthesis by Zileuton (not commonly used as it may cause hepatotoxicity).
2- Competitive antagonists of cysteinyl leukotriene receptors (LTD4 mainly): by Montelukast and Zafirlukast.

Therapeutic uses in bronchial asthma:

1- They are used as Prophylactic before exposure to triggering agents (exercise, irritants, NSAIDS , aspirin induced asthma)..
2- They have the following advantages:
1-Montelukast is safely used in children (as young as 6 months)
2-easy administration as they are given orally.

Side effects: -
- microsomal enzyme inhibition. They increase efficacy & toxicity of co-administrated drugs (methylxanthines). -Hepatotoxicity, headache, dyspepsia

7. Anti-IgE monoclonal antibodies:

Preparation: Omalizumab: 150-375 mg sc injection /2-4 weeks.

- Omalizumab is a new drug that inhibits the binding of IgE to mast cells and prevents mast cell degranulation. It may also inhibit IgE synthesis by B cells.
- They are used in between attacks in corticosteroid resistant patients.
- They are not effective in acute attacks because they do not affect already formed inflammatory mediators

❖ **Drugs Contraindicated in Bronchial Asthma**:

1- NSAIDs (except paracetamol=acetaminophen).
2- Non-selective -Blockers (Propranoloi-Nadoloi-Timoloi-Sotaloi-OxprenoloiPindolol).
3- ACE inhibitors as Captopril.
4- Morphine (depresses R.C., cough centre, and releases histamine).
5- Muscarinic agonists = Parasympathomimetics (Carbachol-Bethanechol,Pilocarpine-Physostigmine-Neostigmine).
6- Other drugs: Histamine liberators as morphine-curare-trimetaphan-Histamine like drugs as phentolamine and tolazoline-Barbiturates (due to depression of R.C.).

❖ **Management of a Case of Bronchial Asthma**

1. **Acute Attacks:**
   - **Drug Used:** Short acting selective B2-agonist (asthma relievers) as salbutamol or Terbutaline.
   - Route of administration: Inhalation.
   - **If no response to selective B2-agonists:**
   - **Drug Used:** Aminophylline. Route of administration: Slowly IV injection. Dose: 250-500 mg.

❖ **Acute severe asthma = Life-threatening asthma (Status asthmaticus}:**

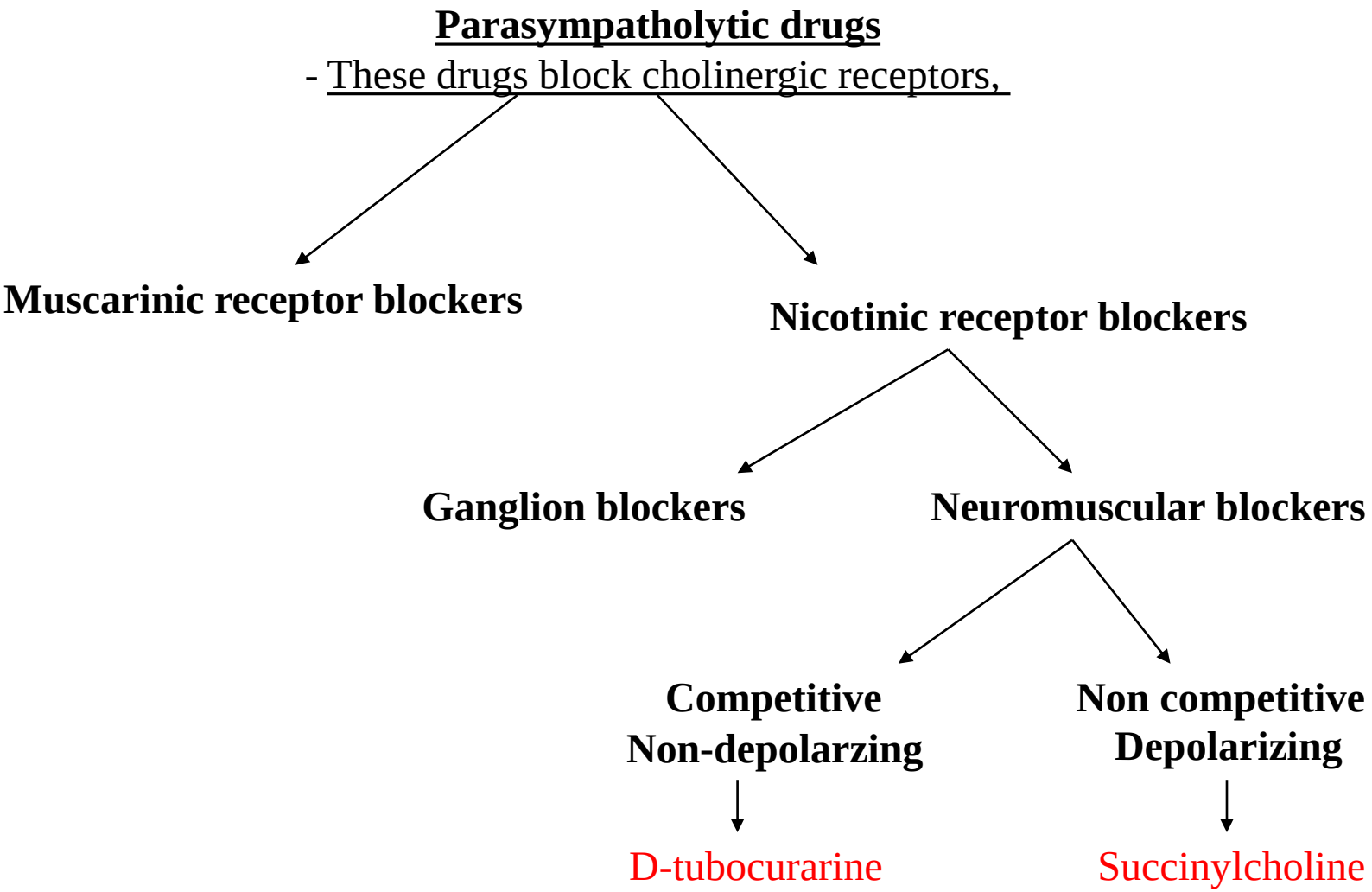
- It is characterized by severe dyspnea, cough, wheezes, cyanosis, sweating, tachycardia, and exhaustion.
- **Management should include:**
  1) Hospitalizations
  2) Oxygen therapy (40-60%).
  3) Hydrocortisone 200 mg. IV /4-6 hours or Methylprednisolone IV for 24 hours followed by oral prednisolone (30-60 mg.) for 2 weeks.
  4) IV fluids as glucose 5% to correct dehydration and for nutrition.
  5) Salbutamol or terbutaline inhalation by nebulizer.
  6) Aminophylline IV infusion (250 mg. IV infusion over 20 minutes).
  7) Antibiotics (to treat associated chest infection e.g. Azithromycin).
  8) Anxiolytics (benzodiazepines -as diazepam-are safe as they do not depress R.C.).

Neuromuscular blockers And Drugs used for Glaucoma

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Neuromuscular blockers



Neuromuscular blockers:

- Block nicotinic receptors on skeletal muscles at neuromuscular junction → muscle relaxation.

	Competitive(non depolarizing)	Non competitive (Depolarizing)
Mechanism of action	They block Nm receptors at neuromuscular junction by competition with acetylcholine at NM receptors	They bind to Nm receptor → initial depolarization (Stimulation &Twitches) followed by maintained depolarization (Block & Paralysis).
Action	Muscle relaxation in: face and neck→ Limb & Trunk → intercostal→ Lastly the Diaphragm.	Initial contraction followed by progressive relaxation of skeletal muscles: arm →leg then neck & face →Diaphragm→ then intercostal
Nn receptors	Inhibition leading to ganglion blockade (hypotension, tachycardia)	Stimulation leading to hypertension and increase GIT motility
Releaser	Histamine releasers cause Bronchospasm,hypotension -Norepinepthrin releasers cause hypertension	**-No**
Preparations	**Short acting (less than 10 minutes):** mivacurium due to inactivation by psudocholineesterase **Intermediate acting (10-20 minutes):** due to extensive hepatic metabolism (atracurium , vecuronium ,cisatraccuonium rocuronium). They have mild histamine release **Long acting**: no hepatic metabolism excreted unchanged in urine. They are divided into 1-Potent histamine releasers , mild ganglion blockers :D-tubocurarine , mecholine . 2-Potent ganglion blockers, mild histamine releasers (tachycardia):Fasidenium , gallamine , alcuronium 3-Norepinepinephrine releasers (hypertension) Pancuronium, pipracuronium, doxacurium	Succinylcholine; **short acting** due to metabolism by plasma pseudocholineesterase

	Competitive (non depolarizing)	Depolarizing (non competitive)
P.K.	- Not effective orally (quaternary amines). Injected I.V . Dose not pass B. B. B. & placenta	
	-Atracurium: spontaneous plasma hydrolysis. Breakdown products may cause seizures. - Mivacurium: Pseudo-Ch.E -Vecuronium: liver.	-Plasma pseudo ChE enzyme
Therapeutic uses	**-Long & intermediate acting (10-20 minutes):** - Adjuvant during general anesthesia -Treatment of convulsive states e.g. tetanus. -Induction artificial respiration to block normal respiratory movements -Short acting(Mivacuronium)is used like succinylcholine	-Facilitate Endoscopy e.g. Endotracheal intubation -Electroconvulsive therapy to reduce muscle injury. -Diagnosis of Myasthenia gravis.
Side effects	-**Hypotension** due to histamine release and ganglion blockade, **Bronchospasm** due to histamine release -**Hypertension** due to increase norepinephrine release (Pancuronium , pipercuonium , doxacuronium)	-**Hypertension** due to sympathetic ganglion stimulation, -Succinylcholine apnea**: prolonged respiratory depression** due to congenital deficiency of psudocholineesteras Treated by: artificial respiration , fresh plasma transfusion (provide pseudocholineesterase), neostigmine -**Vomiting** due to contraction of abdominal muscles

	Competitive (non depolarizing)	Depolarizing (non competitive)
Side effects	-**Overdose causes prolonged respiratory depression**. (treated by atropine and neostigmine) - Atracuronium undergo partial non-enzymatic spontaneous metabolized to toxic tertiary amine metabolite laudanosine which causes CNS stimulation & epilepsy by blocking GABA receptors and hypotension by α1 blocking action	-**Increase intraocular pressure** due to contraction of lid and extraocular muscles -**Muscle injury and hyperkalemia** , - **Malignant hyperthermia** due to initial muscle contraction treated by dantrolene.
Reversed by	Neostigmine (antidote), Tetanic contraction, potassium	Skeletal muscle relaxant effect is reversed by local anesthetics &general anesthetics, quinidine &procainamide, aminoglycosides and polymexine
Augmented by	General and local anesthetics antibiotics (aminoglycosides and polymexin.	- Skeletal muscle relaxant effect is potentiated by neostigmine ,tetanic contraction and potassium. -Decrease in pseudochoineesterase either congenital , hepatic impairment or nutritional deficiency
Contraindication	-Bronchial asthma. -Myasthenia gravis.	- Glaucoma - Congenital deficiency of pseudo ChE enzyme

Drugs acting on the eye

Autonomic supply of the eye

Sympathetic

- Stimulation dilator pupillae muscle (DPM) α1-receptors → active mydriasis
- ↑ aqueous formation (secretion) (B2) → ↑ IOP
- ↓ lacrimal secretion(B1)
- V.C of conjunctival blood vessels (α 1)

Parasympathetic

- Stimulate Constrictor Papillae Muscle (CPM) → miosis
- ↑ Spasm of ciliary muscle → open canal of schlemm→ ↓ IOP
- Accommodation of near vision.
- ↑ Lacrimation secretion

Miotics

- Drugs which produce construction of the pupil.(Miosis): (↑ Parasympathetic or ↓ Sympathetic)

1- Parasympathomimetics:

- Stimulate Constrictor Papillae Muscle (CPM) → miosis.
- ↑ Spasm of ciliary muscle → open canal of schlemm→ ↓ IOP
- Accommodation of near vision.
- ↑ Lacrimation.
- Congestion. (VD)

Preparations:

- Direct acting: as Bethanichol (M only) - Carbachol (M&N) - Pilocarpine (M only).
- Indirect acting: as - Physostigmine (reversible) - Echothiophate (irreversible)

Therapeutic Uses → All given as eye drops in:

- Counteract the effect of mydriatics.
- Treatment of acute and chronic glaucoma. Due to ↓ IOP.
- Break the adhesion between iris and lens. (in alteration with mydriatics)

Miotics

2- Sympatholyics

1. guanthidine
   - Act by ↓ release of endogenous NE → paralysis of DPM → Passive miosis → ↓ IOP.
   - It can be used as eye drops in the treatment of glaucoma.

3- **Central miotics**.

- They act by stimulation of the 3 rd nerve nucleus e.g. morphine → Severe miosis (pin point pupil) is a diagnostic sign for morphine poisoning.

Mydriatics

Drugs that cause widening of pupil (↑Sympathetic or↓ Parasympathetic)

Sympathomimetic & cocaine	parasymatholytic
- They act by contraction of DPM (α1-receptors → active mydriasis with no cycloplegia. (Not cause glaucoma)	- They act by relaxation of sphincter papillary muscle (M.R. blocker) → passive mydriasis with cycloplegia (paralysis of accommodation) → blurring of vision. (cause glaucoma)
- No effect on IOP (Balance in: - B.V. →V.C (α1)→ Decongestion & ↓ IOP - ↑ aqueous formation (B2) → ↑ IOP	- They may be associated with ↑ IOP as a result of ↓ aqueous drainage due to paralysis of ciliary muscle →↓ opening of canal of Schlemm.
- The mydriatic effect is antagonized by α blockers	- The mydriatic and cycloplegic effect is antagonized by physostigmine and pilocarpine
Preparations -α stimulants: Epinephrine -Phenylephrine -Norepinephrine uptake inhibitors: :Cocaine	**Preparations** Duration Aropine 7-10 days Homatropine 1 day Cyclopentolate 1 day Tropicamide 6 hours
Therapeutic use: Fundus examination specially in elderly patients liable for glaucoma	**Therapeutic Uses:** -Atropine in Iritis & Corneal Ulcer. - Synthetic substitutes in Fundus examination

Treatment of glaucoma

1- Closed (Narrow) angle glaucoma (Acute congestive) = Medical emergency

- It is due to sudden closure of aqueous drainage.

Treatment

1**. Dehydrating agents= Osmotic Agents** :

- As: Mannitol by I.V infusion or Glycerin (Orally . (↑ Excretion of fluids outside the eye)

2. **Carbonic anhydrase inhibitors**: (↓ Synthesis of aqueous humor)

- As: Acetazolamide & dorzolamide. (Used orally and as eye drops)

3. Parasympathomimetics:

- As: pilocarpine 3% eye drops 2 drops every 5 minutes. If no response after 2-3 hours ,emergency surgery
- physostigmine
- ↑ aqueous drainage through miosis and widening of canal of Sclemm.

Treatment of glaucoma

2- **Open angle glaucoma** (Simple chronic)

- It is due to↑ aqueous formation as a result of ↑ blood flow to anterior chamber.

Treatment

1. **β-Blockers:**
   - Block β-receptors → ↓cAMP → ↓Formation of Aqueous humour
   - as Timolol (non-selective) & Betaxolol (B2 selective). eye drops. They may cause hypotension and bradycardia due to systemic absorption.

2. Carbonic Anhydrase Inhibitors:

- As: Acetazolamide & Dichlorphenamide (orally)
  and Dorzolamide & Brinzolamide (eye drops)

3. **Miotic Eye Drops:**

- Short Acting →Pilocarpine or Physostigmine

4- **Guanthidine eye drops**.

- Miosis → ↑ drainage of aqueous humour

Treatment of glaucoma

2- **Open angle glaucoma** (Simple chronic)

5- α2·Agonists:

- α2-agonist → ↓ formation of aqueous humor
- As: apraclonidine eye drops

6- Sympathomimetics:

- V.C. → ↓Synthesis of Aqueous humour
- As: adrenaline & Dipivefrin (prodrug)

7- Prostaglandins:

- Prostaglandine → ↑ outflow of aqueous humor
- Latanoprost eye drops.

Autacoids

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Assist. Professor of pharmacology and Toxicology

Autacoids

❖ Autacoids (local hormones)

- Endogenous substances of chemically diverse produced by cells or tissues and act locally hormones to regulate the function of nearby organs

❖ Autacoids are classified according to their chemical structure into:

- **Amino acid derivatives** e. g. histamine and serotonin.
- **Vasoactive polypeptides e**.g. Angiotensin and Kinins
- **Fatty acid derivatives (eicosanoids)** e.g. Prostaglandins and Leukotrienes.

Autacoids

1. Histamine

❑ Synthesis :

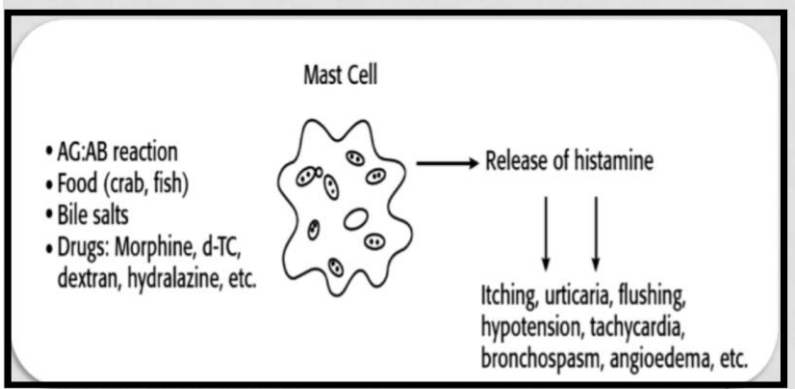
- Histidine (amino acid) $\xrightarrow{\text{histidine decarboxylase}}$ Histamine

❑ Storage:

- In most tissues e.g. lung, skin, stomach & Brain.
- In cells e.g. mast cells and Basophiles

❑ Released

- Hypersensitivity reactions (allergy): Antigen-antibody reactions.
- Destruction of cells (Inflammation).
- Some drugs as morphine, atropine, curare, and hydralazine)


Mast Cell
• AG:AB reaction
• Food (crab, fish)
• Bile salts
• Drugs: Morphine, d-TC, dextran, hydralazine, etc.
Release of histamine
Itching, urticaria, flushing, hypotension, tachycardia, bronchospasm, angioedema, etc.

Autacoids

❑ Histamine receptors and effects

Type	Location	Function
H_{1-} receptor	- Blood vessel - Skin, Sensory nerve - Smooth muscle - Brain	- Release of NO →**Vasodilatation** → hypotension & edema, redness. - **Sensory nerve stimulation**→ pain & itching **.** - **Smooth muscle contraction** → Bronchospasm & GIT contraction, uterus contraction - **Stimulation of secretion:** lacrimal, nasal, branchial secretion. - **In C.N.S** → CTZ (vomiting, vertigo and motion sickness). Sensory centers, alertness
H_{2-} receptor	in gastric mucosa & heart,	- ↑ gastric HCL secretion - ↑ cardiac contractility and HR.
H_{3-} receptor	CNS and presynaptic autoreceptors	- Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin

❑ Histamine antagonist by:

- Physiological antagonism (e.g., Adrenaline).
- Inhibit the release of histamine (mast cell stabilizer e.g., cromolyn & ketotifen).
- H-receptors blocker (H1-H2 blocker)

❖ Antihistaminic drugs

❖ H1- receptor blocker:

First generation	Second generation
- Pass to BBB, H1 blockers & M blocker receptor, short duration of action (4-6 h)	-No pass BBB, H1 blockers, prolonged duration action/ 12–24 h
- They cause sedation effects	No
- Relieve vomiting (antiemetic effect, motion sickness) & antiparkinsonian effects.	No
- Atropine like action (blurring of vision , dryness of secretion , dry mouth, constipation and urinary retention	No
- Relief of itching, pain and allergic response. - ↓ capillary permeability and inflammatory edema induced by histamine - ↓ bronchoconstriction, bronchial secretions, lacrimation, etc.	

First generation	Second generation
Therapeutic uses: - Antiallergic(treatment of Rhinitis, Urticaria & common cold preparations, atopic dermatitis, angioedema.) - Antiemetic, relive of motion sickness (2nd choice), Meniere's disease and Parkinsonism (Promethazine, diphenhydramine, Meclizine , cyclizine) - Sedative (doxylamine & diphenhydramine)	**Therapeutic uses** - Antiallergic(treatment of allergy & itching) - They can be used topically
Side effects -Sedation in therapeutic doses -CNS stimulation (hallucination and convulsions) in toxic doses due to atropine like action	**Side effects** -Cardiac arrhythmia in large doses -Drug allergy -Cetirizine produces mild sedation because it partially passes to BBB

First generation	Second generation
Preparations: -**Diphenhydramine , dimenhydrinate**: potent sedatives and atropine like action -**Promethazine**: potent sedatives and atropine like action+ alpha adrenergic blocker (postural hypotension) -Chlorpheniramine, brompheniramine , clemastine: moderate sedation -Meclizine , cyclizine : slight sedation - doxylamine: strong sedation - Cyproheptadine: also 5-HT blocker	**Preparations** -Loratadine -Cetirizine -Fexofenadine, desloratadine & Levocetirizine : more potent and less cardiac arrhythmia - Ketotifen is a 2nd gen H1 blocker and mast cell stabilizer

NB: Doxylamine: used for vomiting & morning sickness during pregnancy (combined with Vit B6)

❑ Drug interactions:

- MAO inhibitors → ↑ anticholinergic effect.
- Anxiolytics and hypnotics →↑ effect of H1 blockers on CNS→ more sedation.
- Cholinesterase inhibitors → ↓ effect of cholinergic

❖ H2- receptor antagonists:

❑ Preparation:

- **Cimetidine** (not widely used due to dangerous side effects)
- **Ranitidine** (Zantac)® & **Nizatidine** (150mg bid or 300mg at bedtime)
- **Famotidine** (most potent, 20mg bid or 40mg at bedtime).

- Act mainly on GIT by blocking H2 receptors → decrease secretion of gastric acids (HCl and pepsin)

- Cimetidine has anti-androgenic effects → Gynecomastia and infertility and loss of sexual desire in males, HME inhibitor

- Inhibition of histamine release in the CNS: confusion , hallucination and headache

- Given orally and parenterally.

❑ Therapeutic uses:

- Gastric ulcers & duodenal ulcer (reduce nocturnal acid secretion, accelerate healing)
- GERD, Heart burn (PPI are preferred).
- Zollinger- Ellison Syndrome. (PPI are preferred).

❑ Side effects with cimetidine:

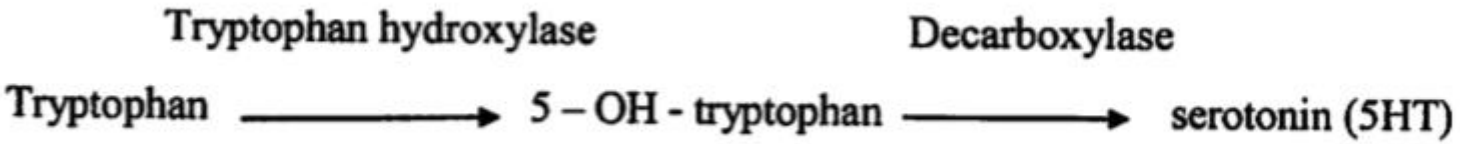
- Anti-androgenic action→ impotence, gynecomastia in men and galactorrhea in women.
- CNS disturbances → confusion.
- HME inhibitor→ ↑ action of other concomitant drugs.
- **Side effects of other H2-blockers**: diarrhea, headache and fatigue.

Autacoids

Cimetidine	Ranitidine	Famotidine	Nisatidine
-Weak H2 blocker	-Potent H2 blocker	Long acting H2 blocker, most potent	Rapidly acting H2 blocker
Potent microsomal enzyme inhibitor	Weak microsomal enzyme inhibitor	No effect on microsomal enzymes	No effect on microsomal enzymes
Potent inhibitor to male sex hormones	No effect on male sex hormones	No effect on microsomal enzymes	No effect on microsomal enzymes
CNS side effects	Less CNS side effects	Less CNS side effects	Less CNS side effects
-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis -Treatment of hisutism	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis	-Used in treatment of peptic ulcer , duodenal ulcer , heart burn , reflux esophagitis

2. Serotonin (5-hydroxytryptamine, 5-HT)

- **Synthesis:**



- **Metabolism:** By MAO into 5-hydroxyindole acetic acid;"5HIAA".in urine, Used in diagnosis of carcinoid syndrome (excess5-HT).

- **Storage:** GIT enterochromaffin cells, blood (platelets), brain.

- After release from neurons, it is Reuptake into the nerve ending by a serotonin reuptake transporter (SERT).

❑ Actions of serotonin:

- **5-HT1 receptors:** CNS, Blood vessels
  - 5-HT1A: stimulation in the limbic system → **anti-anxiety action**.
  - 5-HT1D, 5-HT1B: stimulation → cerebral vasoconstriction. → used for **acute migraine attack.**

- **5-HT2 receptors**: CNS, Blood vessels, GIT, smooth muscle, platelet
  - Stimulation → causes CNS induction, suppression of appetite, general vasoconstriction and smooth muscle contraction, Hallucinations

- **5-HT3 receptors**: CTZ, sensory nerve
  - Found in CTZ Stimulation → causes nausea, vomiting and pain.

- **5-HT4 receptors**: GIT, CNS
  Found in GIT Stimulation → causes spasms and ↑ gastric emptying → prokinetics effect.

❑ Drugs Affecting Serotonin

1. serotonin receptor agonists:

- **Buspirone:**
  - Selective 5-HT1A agonist (partial agonist)
  - Used orally to treat anxiety with or without depression.

- **Sumatriptan & zolmitriptan :**
  - Selective 5-HT1B & 5-HT1D agonist.
  - Used in acute migraine.
  - More effective than ergotamine.
  - Nausea, chest pain and coronary vasospasm are the main side effects.
  - Contraindicated in pregnancy and peripheral vascular diseases.

- **Ergotamine:**
  - 5-HT1D & α1-receptors partial agonist → VC.
  - Treats acute migraine (Poorly absorbed orally (caffeine ↑ oral absorption).
  - Spasmogenic effect on smooth muscles of uterus (oxytocic effect) and CTZ → Nausea and vomiting.
  - Hypertension, anginal pains, Nausea & vomiting, Abortion is the common adverse effect.
  - Contraindicated in pregnancy and peripheral vascular disease.

- **Ergometrine:**
  - 5-HT2 & α1 partial agonist.
  - Stimulates uterine smooth muscle contraction → oxytocic action.
  - Used also for treatment and prevention of postpartum hemorrhage.
  - Given orally and parenterally.

- **Metoclopramide & Domperidone**:
  - Act centrally by blocking D2 receptors in CTZ → ↓ nausea and vomiting
  - Act peripherally by 5-HT4 agonists → ↑ GIT motility and used for treatment of vomiting & GERD

- Tegaserode- → 5-HT4 agonists → prokinetic → in irritable bowel syndrome (IBS) with constipation

- Cisapride, mosapride: gastroprokinetic by 5-HT4 agonists & ↑Ach release → ↑ GIT motility used in gastroesophageal reflux disease [GERD], IBS.

- **Selective serotonin reuptake inhibitors** (SSRIs): Fluoxetin , Sertralin
  - inhibiting 5-HT reuptake → ↑ serotonin action, ↑central 5-HT→ used in depression

2. serotonin receptor antagonists:

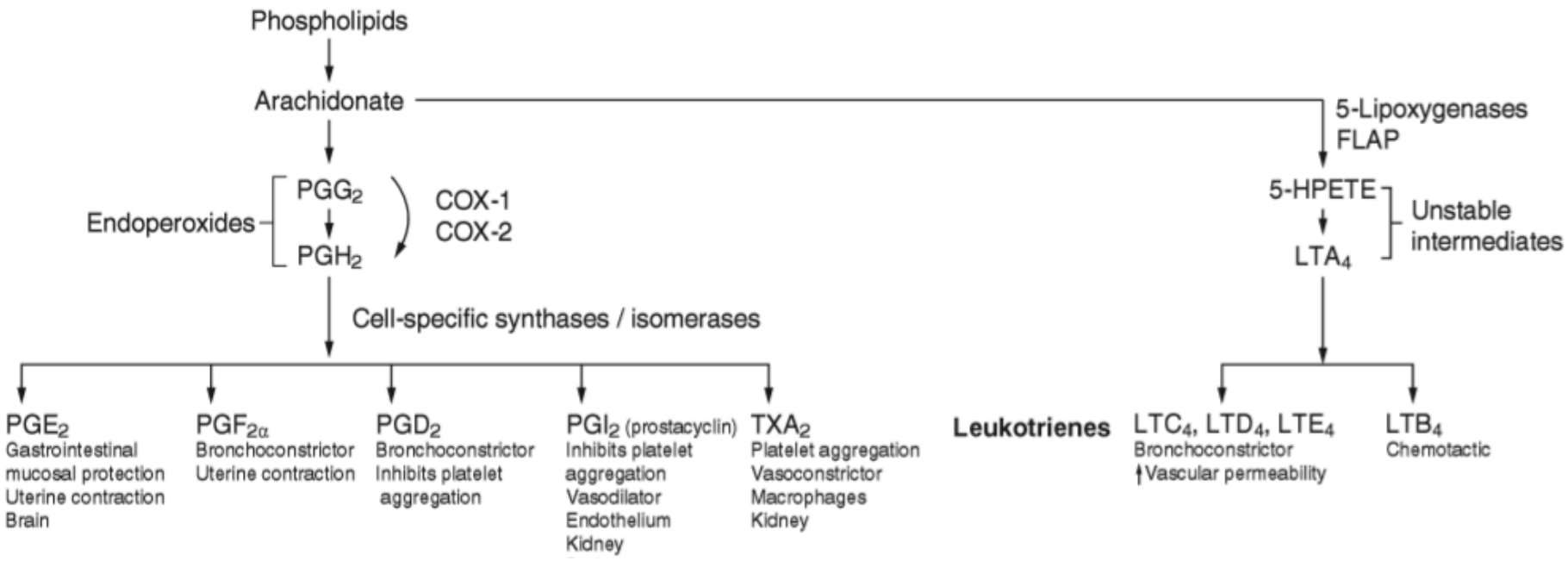
- **Cyproheptadine & Pizotifen** (Mosegor)®
  - 5-HT2 & H1- M receptors antagonists.
  - Used as appetizer, in allergy and for prophylaxis of migraine.
  - Sedation and dry mouth are the main side effects.

- **Ondansetron & Granistron**:
  - Selective 5-HT3 blockers.
  - Used orally and parenterally for prevention and treatment of nausea & vomiting associated with surgery and cancer chemotherapy.
  - Headache is the common side effect.

- **Ketanserin:**
  - Selective 5-HT2 blocker.
  - Causes mixed VD and prevent platelet aggregation.
  - Also has selective blocking for α1, H1 and dopamine receptors.
  - Used for treatment of hypertension and peripheral vascular diseases.

3. Eicosanoids

- They include prostaglandins (PGs) and Leukotrienes (LTs).
- They have very short duration of action.
- They are synthesized & released as required. Not stored in body.
- Synthesized in all cells from arachidonic acid.
- Arachidonic acid is synthesized from cell membrane phospholipids:



Biosynthesis of Eicosanoids

1. Prostaglandins:

- Prostaglandins (PGs) are products of long-chain fatty acids.
- Arachidonic acid is the precursor for the biosynthesis of all PGs.
- The enzyme involved in the formation of PGs from arachidonic acid is cyclooxygenase (COX).
- The main PGs in humans are prostaglandin E2 (PGE2), prostaglandin F2 (PGF2) and prostacyclin (PGI2).

- Types of COX:
  a-COX-1: Physiological (constitutive) → Renal VD & ↓ Gastric HCI.
  b-COX-2: Pathological (Inducible) → Inflammation:
  - Bacterial infection-+ Toxins → PGE2 → Hypothalamic HRC → Fever.
  -.Sensitize Nociceptors to Bradykinin, Histamine & 5-HT → Pain.
  -Potentiate Bradykinin & Histamine → VD, ↑ Capillary permeability → Edema.

❖ Pharmacological actions and uses

1. On CNS:

- PGE2 → Fever & pain
- Inhibited by **NSAIDs** (analgesics & antipyretics)

2. Inflammation:

- PGE2 & PGI2 → Potentiate B. k. & Histamine → VD (hotness), ↑ Capillary permeability → Edema & ↑ pain

* Inhibited by NSAIDs and glucocorticosteroids → analgesic & anti-inflammatory.

3. On CVS:

- TXA2 & PGF2α → vasoconstriction
- PGI2 & PGE2 & PGE1 → vasodilatation → hypotension.
  a. PGE1 (alprostadil) → used to maintain the patency of ductus arteriosus before surgery.
  b. Prostacyclin (PGI2) → ↓ peripheral, pulmonary and coronary resistance.
  PGI2 (epoprostenol) → used to treat pulmonary hypertension.

.**Platelet Function:** Balance between

- PGI2 → ↓ platelet aggregation.
- TXA2 → ↑ platelet aggregation. (inhibited by low dose aspirin, Antithrombotic effect)

3. On GI tract:

- PGE1 & PGE2 → ↓ HCl secretion, ↑mucous secretion, ↑ Blood supply & ↑ Healing of ulcer, (cytoprotective action) and ↑ gastric motility.

Misoprostol (PGE1 analogue) → used for the prevention of NSAID-induced ulcers

4. **On Eye:**

- PGF2α → ↑ Outflow of aqueous humor → ↓ intraocular pressure.
- Latanoprost, travoprost (PGF2α analogue)→ used as eye drops in glaucoma.

5. **On sex organs:**

a) Uterus:

- PGF2a & PGE2 → ↑ contractility and motility uterine &dilation of cervix → Oxytocic action. (Used to induce labor and abortion)
- Misoprostol & Dinoprostone (synthetic analog of PGE1 & PGE2)
- Carboprost (synthetic analog of PGF2α)

b) Male reproductive system: PGE1 → VD of male genital organs and transport of sperms. (Used for impotence)

- Alprostadil (PGE1) used for erectile dysfunction.

6. On bronchi:

- PGF2α & TXA2 → Bronchospasm.
- PGE1 & PGI2 → Bronchodilatation. (may be used in bronchial asthma)

7. On kidney:

- PGI2 & PGE2 →VD → ↑ RBF → increase renin secretion.

❖ Adverse effects of PG analogs

1. Latanoprost → gradual change in iris color- keratopathy- cornal erosion (rare)
2. Dinoprostone & misoprostol → diarrhea.
3. Carboprost → bronchospasm
4. Alprostadil → penile pain, urethral burning, vaginal itching in partner (locally) , dizziness & tachycardia (if absorbed systemically).

Autacoids

Actions	Uses of PG	Uses of NSAID
1- Mechanism → G-protein coupled receptors		
1- C.N.S.: a- Hypothalamus → HRC → Fever b- Thalamus → Pain		- Antipyretic - Analgesic
2- Eye → ↑ Outflow of Aqueous Humor → ↓ IOP	Open angle glaucoma (*Latanoprost* Eye drops)	
3- Peripheral → Inflammation		- Anti-inflammatory
4- Immunomodulating → ↓ T-lymphocytes		
5- C.V.S.: a- Maintain patency of Ductus Arteriosus b- B.V. → Most of them → V.D. → TXA-2 → V.C. c- Platelets → PGI-2 & PGD-2 → ↓ PA → TXA-2 → ↑ PA	-Maintain patency in transportation of vessels *(Alprostidil I.V. Infusion)* - PVD *(Epoprostenol & Iloprost I.V. Infusion)* - Antiplatelet agent *(Epoprostenol & Iloprost)*	- Patent ductus srteriosus without transportatioin of big vessels - Antiplatelet
6- Bronchi → PGE-2 → Dilatation → PGF-2α → Constriction	- Bronchial asthma *(PGE-2)*	
7- G.I.T. : a- Stomach: ↓ HCl, ↑ HCO_3, ↑ Mucus, ↑ Blood supply & ↑ Healing b- Intsetine → ↑ Motility	- NSAID induced peptic ulcer *(Misoprostol & Enprostil)*	
8- Kidney: V.D. & ↑ Renin		
9- Sex organs: a- Females: Uterine contractions b- Males: Erection & Motility of sperms	- Labor, abortion & contraception *(Dinoprost, Dinoprostone, Gemeprost & Carboprost)* - Improve erection & fertility	- Dysmenorrhea & premature labor

2. Leukotrienes:

❑ Actions of leukotrienes:

a) LTC4, LTD4 & LTE4 → slow reacting substances of anaphylaxis.

- Powerful bronchospasm (1000 times > histamine) and ↑ bronchial secretion. → important mediators of bronchial asthma.
- Present in sputum of patients with asthma, chronic bronchitis & allergic rhinitis

b) LTB4 = Potent chemotactic factor. → important mediator of inflammation.

* Increase production of reactive oxygen species.

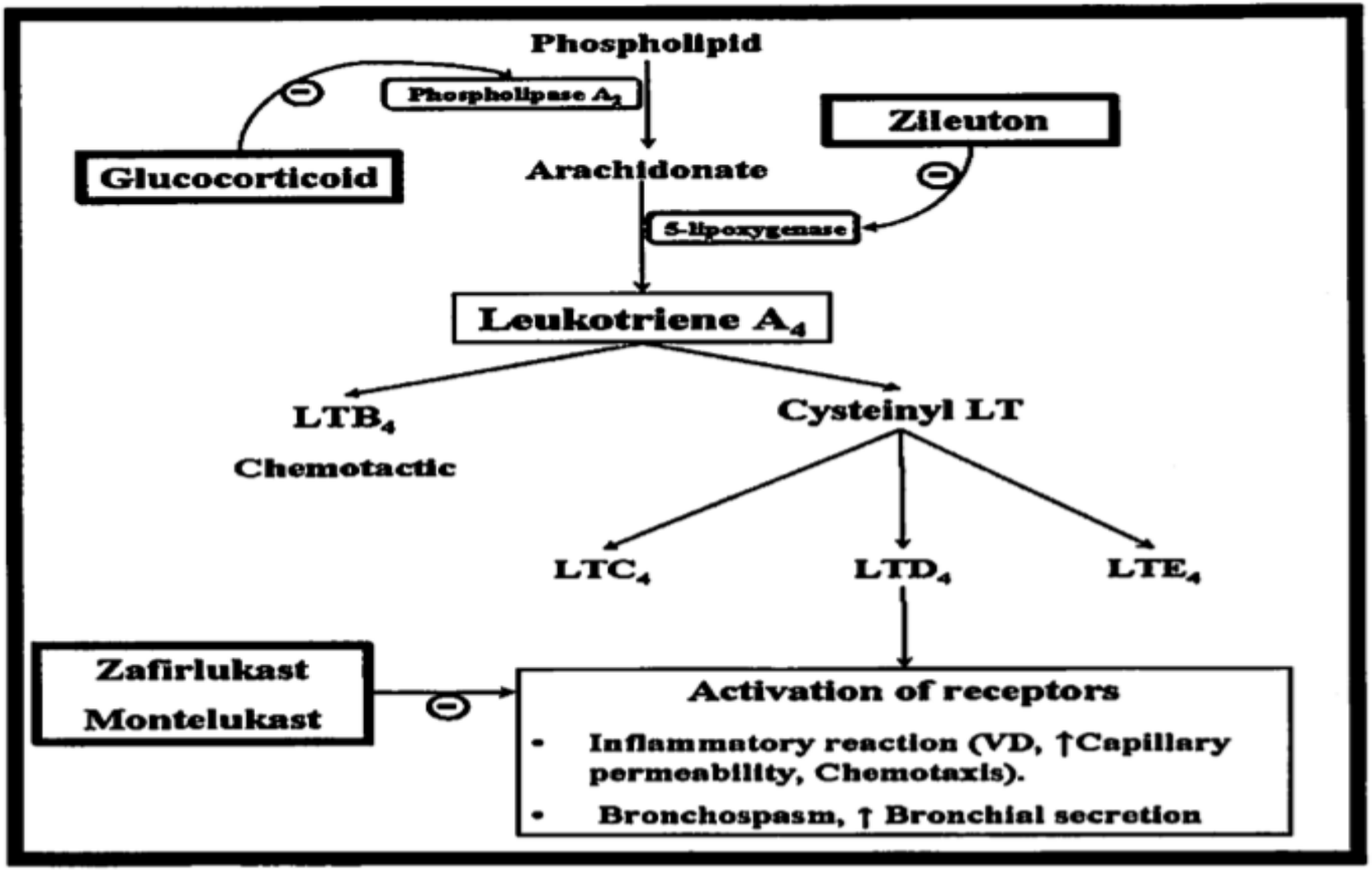
❑ Inhibitors of LTs include:

1.Lipooxygenase inhibitors: zileuton.

2. LT receptor antagonists: zafirlukast and montelukast.

- Used orally for prophylaxis of bronchial asthma.

Autacoids


Phospholipid
Phospholipase A2
Glucocorticoid
Arachidonate
Zileuton
5-lipoxygenase
Leukotriene A4
LTB4
Chemotactic
Cysteinyl LT
LTC4
LTD4
LTE4
Zafirlukast
Montelukast
Activation of receptors
• Inflammatory reaction (VD, ↑Capillary permeability, Chemotaxis).
• Bronchospasm, ↑ Bronchial secretion

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